



# FEDERATION PROCEEDINGS

VOLUME 6

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1947





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Program of Thirty-First Annual Meeting, Chicago, Illinois, May 1947

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# FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

PROGRAM 1947

Chicago, May 18, 19, 20, 21, 22

## GENERAL INFORMATION

In spite of rising costs and the uncertainties of the post war period the Local Federation Committee has succeeded in obtaining sufficient hotel accommodations in Chicago to hold the meeting as planned. Since the procurement of hotel rooms was the greatest bottleneck, the convention dates, the banquets and dinners, and even the comfort and convenience of the visiting scientists have, in many instances, been subjugated to the need for more hotel rooms. Thus, Sunday registration and occupancy of hotel rooms has been stipulated by the hotel managements. The dinners, luncheons, and banquets have been used as bartering agents to obtain a greater allotment of rooms from the respective hotels. This has resulted in lack of centralization of the dinners and in some instances an actual increase in the cost of the individual functions has occurred. The Local Committee thus regrets that this will probably be the most expensive meeting which the members have attended.

The meeting days are Sunday May 18, 19, 20, 21, and 22 (Thursday). The official hotels are the Stevens and the Congress. Sunday afternoon and evening will be devoted to registration, Council and Executive Committee meetings of the various societies.

### Hotels

As previously announced, the Hotel Committee completed its duties on April 15, the following reminders are in order: (1) Any late changes in hotel rooms such as cancellations or changes in time of occupancy must be taken up directly with the hotel involved. (2) Bring your confirmation of hotel reservation so that your occupancy of the hotel room can be expedited.

### Registration

Members who have registered in advance by mail may claim their badges at the registration counter. The official registration counter is located on the mezzanine floor of the Hotel Stevens, and is open from 1 to 9 p.m. on Sunday, May 18, and 8:30 a.m. to 4:30 p.m. thereafter except Thursday when the hours are 8:30 a.m. to 2 p.m. The registration fee is \$3.00. Admission to scientific sessions will be strictly limited to those who are wearing official registration badges. Programs, preprints, and tickets to smokers and special functions will be on

sale at the registration counter. An information center will also be available at the registration desk. Members of any of the constituent societies, physicians, graduate students or workers in biological laboratories may register and participate in the scientific sessions.

### Informal Smoker

The Federation Smoker will be held in the Ballroom of the Stevens Hotel on Wednesday evening, May 21, 8 p.m. to 1 a.m. Refreshments will be served. Admission to the Smoker will be by individual tickets (price \$1.00 plus tax) which will be available for all registrants at the Registration Desk up to Wednesday afternoon. Any remaining tickets will be on sale at the door on Wednesday evening.

### Local Committee

The University of Illinois is acting as the host institution to the Federation. The Local Federation Committee has made all arrangements for the convention, and functions with the following officers and subcommittee chairmen:

G. E. Wackerlin (Illinois), chairman, C. C. Pfeiffer (Illinois), secretary treasurer, C. I. Reed (Illinois) Registration, E. A. Evans, Jr. (Chicago), Program and Scientific Meetings, R. W. Gerard (Chicago), Public Information, L. N. Katz (Michael Reese), Entertainment, R. C. Ingraham (Illinois), Projection Service, H. C. Wiggers (Illinois), Static Demonstrations, W. Van Winkle, Jr. (Amer. Med. Assoc.), Motion Picture Exhibits, J. Sendroy (Loyola), Communication Service, Mrs. C. I. Reed, Women's Reception.

Other members of the Local Committee are: H. H. Beard, G. A. Bennett, Olaf Bergheim, T. E. Boyd, W. J. R. Camp, P. R. Cannon, I. Davidson, C. A. Dragstedt, C. J. Farmer, E. M. K. Geiling, J. S. Gray, C. G. Hartman, A. C. Ivy, K. K. Jones, L. N. Katz, A. B. Luckhardt, W. S. McCulloch, Rafael Mendez, L. B. Nice, Thelma Porter, W. C. Rose, J. P. Simonds, Samuel Soskin, W. R. Tweedy, W. H. Welker.

### Static Demonstrations

Static demonstrations will be held at the University of Illinois College of Medicine, 1853 West Polk Street (approximately 2½ miles due west of the Stevens Hotel) on Tuesday afternoon (2 to 6 p.m.)

and evening (7 to 10 p m ) For convenience, use the entrance at 1853 West Polk Street The following suggestion is given as the preferable mode of transportation to the University Taxi (10 minutes)—rates circa \$0 70 for the first passenger plus five cents for each additional rider For further details regarding elevated trains, buses, streetcars, and automobile routes, information can be obtained at the Information Desk

#### *Women's Reception, University of Illinois*

A conducted tour of the Research and Educational and affiliated Hospitals and the professional colleges of the University of Illinois is planned by the Women's Reception Committee for visiting wives and their friends Tours are scheduled from 2 00 to 3 15 p m on Tuesday afternoon, May 20, and an informal tea and reception will also be held from 3 30 to 5 00 p m on Tuesday at the Chicago Illini Union Building

#### *Other Institutions*

Members of the Federation in the Chicago area cordially invite their colleagues to visit with them and the institutions with which they are associated while attending the meetings

*Placement Service* The Executive Officer of the Federation Placement Service, Dr Howard B Lewis, will be available for consultation at the Federation Headquarters on Sunday, May 18 Appointments may be made through the secretary on duty there All applicants for positions are requested to prepare a typed statement including age, marital status, educational, academic and research backgrounds, references and publications, and to send a copy of this in advance of the meetings to Dr Lewis at the Medical School, University of Michigan, Ann Arbor, Mich Another copy should be brought by the applicant to the interview

# FEDERATION PROGRAM

## JOINT SESSION OF THE FEDERATION

Monday 1 45 p m

GRAND BALLROOM, STEVENS HOTEL

A Baird Hastings, *Presiding*

- 1 Vincent du Vigneaud, *Cornell University*  
Synthetic Penicillin
- 2 C N H Long, *Yale University*  
The conditions associated with secretion of the adrenal cortex
- 3 A D Welch, *Western Reserve University*  
Present status of pteroylglutamic acid and other hematopoietic agents
- 4 A M Pappenheimer, Jr, *N Y University*  
Bacterial Toxins

## MOTION PICTURES

Monday, 7 00-11 00 p m

UPPER TOWER ROOM, STEVENS HOTEL

Thursday, 1 00-5 00 p m

ROOM 14, PALMER HOUSE

- 1 Abraham Goldin (*introduced by Stephen Krop*), *Medical Division, Edgewood Arsenal, Maryland*  
On the neurological effect of some chlorinated tertiary amines
- 2 R P Walton, O J Brodie (*by invitation*) and M Belkin (*by invitation*), *Medical College of the State of South Carolina, Charleston, South Carolina*  
Effect of drugs on the heart *in situ* (24 minutes)
- 3 J R Poppen, Capt (MC), USN, and E S Mendelson (*introduced by D W Bronk*), *Naval Air Experimental Station, Philadelphia 12, Pa*  
Studies of seat ejection for emergency escape from aircraft
- 4 Otis M Cope and Benjamin Jablons (*by invitation*), *New York Medical College, Flower and Fifth Avenue Hospitals*  
Neutralization by tubulin (renal antipressor substance) of vasoconstrictor action of epinephrin on frog (10 minutes)
- 5 B Etsten (*by invitation*), W A Humwich (*by invitation*) and H E Humwich, *Albany Medical College and Medical Division, Edgewood Arsenal, Maryland*  
Pentothal anesthesia Physiologic basis
- 6 Paul A Nicoll and Richard L Webb (*by invitation*), *Indiana University School of Medicine, Bloomington, Ind*

Vasomotion in peripheral blood vessels (15 minutes)

- 7 Austin H Riesen (*by invitation*) and George Clark, *Yerkes Lab of Primate Biology and Yale University*  
Chimpanzees reared in darkness (20 minutes)
- 8 Ernst Simonson, Josef Brozek (*by invitation*) and Ancel Keys *Lab of Physiological Hygiene, Univ of Minnesota, Minneapolis*  
Visual Fatigue (10 minutes)
- 9 A A Ward, Jr (*by invitation*), W S McCulloch and H W Magoun, *Dept of Psychiatry, Univ of Illinois College of Medicine, and Dept of Anatomy, Northwestern Univ Medical School*  
Tremor at rest in the monkey (10 minutes)
- 10 Hiram E Essex and A Grana (*by invitation*), *Mayo Clinic, Rochester, Minn*  
Transient leucopenia produced by an intravenous injection of a number of substances
- 11 Martin B Macht (*introduced by H S Belding*), *The Quartermaster Corps, Climatic Research Lab, Lawrence, Mass, and Dept of Physiology, Johns Hopkins University, School of Medicine, Baltimore, Md*  
Autonomous spinal responses to thermal stimuli A study of spinal man (18 minutes)
- 12 A C Corcoran, Don Carlos Hines (*by invitation*) and Irvine H Page, *Research Lab, Eli Lilly Co, Indianapolis Ind*  
Kidney function in health (40 minutes)

## STATIC DEMONSTRATIONS

Tuesday, 2 00-6 00 p m and 7 00-10 00 p m

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE

- 1 Fred F Anderson (*by invitation*) and Bradford N Craver, *Ciba Pharmaceutical Products, Inc*  
A compact coronary perfusion apparatus
- 2 H C Bazett, *University of Pennsylvania Medical School*  
A circulation schema to illustrate control of capillary pressure
- 3 Howard H Beard, Samuel Libert (*by invitation*) and B Halperin (*by invitation*), *Department of Biochemistry Chicago Medical School, Chicago*  
Correlation of a biological test with clinical diagnosis in human malignancy
- 4 H R Catchpole, *Department of Pathology, University of Illinois College of Medicine, Chicago*  
Apparatus for cell fractionation by differential centrifugation

- 5 **Frederick E Emery and Alfred H Lawton** (by invitation), *Department of Physiology and Pharmacology, University of Arkansas*  
The effect of prostigmine methylsulphate on the pelvic symphysis of the guinea pig
- 6 **Walter Flagg** (introduced by Laurence Irving), *Swarthmore College*  
Determination of gases in 0.7 to 0.14 mm<sup>3</sup> of gas
- 7 **Sarah C Flemister** (introduced by Laurence Irving), *Swarthmore College*  
Estimation of CO<sub>2</sub> and O<sub>2</sub> in a 12 mm<sup>3</sup> blood sample
- 8 **Isidore Gersh** (introduced by Carl C Pfeiffer), *Department of Pathology, University of Illinois College of Medicine, Chicago*  
Freezing drying apparatus for the preparation of tissues for histochemical procedures
- 9 **W Knowlton Hall** (by invitation), **V P Sydenstricker**, **Lester L Bowles** (by invitation), **Lane Allen** (by invitation), **J L Berg** (by invitation), and **E R Pund** (by invitation), *Departments of Biochemistry, Medicine, Microanatomy, Anatomy and Pathology, University of Georgia School of Medicine, Augusta, Ga*  
Ocular changes resulting from nutritional deficiencies in the rat
- 10 **Allan Hemingway and E B Brown** (by invitation), *Department of Physiology, University of Minnesota Medical School, Minneapolis*  
The recording oximeter  
**Laurence Irving, P F Scholander** (by invitation) and **Otto Hebel** (by invitation), *Swarthmore College*  
Apparatus for complete recording of respiratory exchange of man
- 12 **Benjamin Jablons** (introduced by Otis M Cope), *Goldwater Memorial Hospital and New York Medical College, Flower and Fifth Avenue Hospital, New York City*  
Angiopathic effect of renal insufficiency
- 13 **W G Kubicek, and F J Kottke** (introduced by M B Visscher), *Department of Physiology University of Minnesota, Minneapolis*  
A shielded silver electrode with mercury leads designed for prolonged stimulation experiments
- 14 **Horace O Parrack, Miles A McLennan, and Edward G Correll** (introduced by H M Sweeney), *Aero Medical Laboratory, Air Materiel Command, Wright Field, Dayton, Ohio*  
The analysis of high frequency sound fields
- 15 **W T Porter and F H Pratt**, *Dorcy and Wellesley Hills, Massachusetts*  
A convertible kymograph with synchronous motor, and a timing pendulum for universal driving current
- 16 **B P Reed** (by invitation) and **C I Reed**, *Department of Physiology, University of Illinois College of Medicine, Chicago*  
Methods of adaptation of x-ray diffraction to the study of bone and dental structures
- 17 **C I Reed and B P Reed** (by invitation), *Department of Physiology, University of Illinois College of Medicine, Chicago*  
Demonstration of the use of the electron microscope and diffraction unit in a study of cellular metabolism
- 18 **C I Reed, Frank Folk** (by invitation) and **Norman R Joseph** (by invitation), *Department of Physiology, University of Illinois College of Medicine, Chicago*  
The intracorporeal determination of pH with a needle electrode
- 19 **Bodil Schmidt-Nielsen** (introduced by Laurence Irving), *Swarthmore College*  
Accurate analysis of 0.4 to 0.1 mm<sup>3</sup> of gas
- 20 **Knut Schmidt-Nielsen** (introduced by Laurence Irving), *Swarthmore College*  
Use of 1 ml syringe burette for titrations in the field
- 21 **P F Scholander** (introduced by Laurence Irving), *Swarthmore College*  
Accurate analysis of respiratory gases in 0.5 cc samples
- 24 **Albert Sobel**, *Chemistry Laboratory, Jewish Hospital of Brooklyn*  
The estimation of vitamin A with activated glycerol dichlorhydrin
- 23 **Albert Sobel, Albert Hirschman** (by invitation) and **Lottie Besman** (by invitation), *Chemistry Laboratory, Jewish Hospital of Brooklyn*  
Improved aeration tube for the determination of ultramicroquantities of urea, Kjeldahl and amino acid nitrogen
- 24 **R P Walton**, *Department of Pharmacology, Medical College of South Carolina, Charleston*  
A novel kymograph drive
- 25 **A A Ward, Jr, W S McCulloch**, *Illinois Neuropsychiatric Institute, University of Illinois College of Medicine, Chicago, and H W Magoun, Department of Anatomy, Northwestern University Medical School, Chicago*  
Monkey with tremor at rest

## THE AMERICAN PHYSIOLOGICAL SOCIETY

## FIFTY-SIXTH ANNUAL MEETING

## PHYSIOLOGY A

Monday, 9 00 a m

PINE ROOM, CONGRESS HOTEL

## Biophysics

- 1 Charles R Noback (*by invitation*), John W Remington and W F Hamilton, *Long Island College of Medicine and the University of Georgia School of Medicine*  
Volume pressure relationships in the human aorta
- 2 J R Pappenheimer, *Harvard Medical School*  
On the distensibility of the arteries
- 3 H Lamport, *Yale University School of Medicine*  
Arteriolar elasticity implications of the validity of Poiseuille's law in perfusion with Ringer's solution
- 4 H G Kobrak (*introduced by* Lester R Dragstedt), *University of Chicago*  
The round window membrane of the cochlea
- 5 Daniel A Brody (*by invitation*) and J P Quigley, *University of Tennessee*  
Some physical factors in receptive relaxation
- 6 Gordon Marsh and Harold W Beams (*by invitation*), *State University of Iowa*  
Electrical control of growth polarity in regenerating *Dugesia tigrina*
- 7 Warren S Rehm, *University of Louisville School of Medicine*  
The effect of applied current on the potential of the resting stomach
- 8 Lowell E Hokin (*by invitation*) and Warren S Rehm, *University of Louisville School of Medicine*  
Relationship between gastric potential and secretion when dilute saline is placed in contact with mucosa
- 9 Peter Kellaway (*by invitation*) and H E Hoff, *McGill University, Montreal*  
Inhibition in the auditory nerve
- 10 H K Hartline, Lorus J Milne (*by invitation*) and I H Wagman, *Johnson Research Foundation, University of Pennsylvania and Jefferson Medical College*  
Fluctuation of response of single visual sense cells
- 11 M H Halperin (*by invitation*), J I Niven (*by invitation*) F J W Roughton (*by invitation*) and R A McFarland, *Boston University School of Medicine, Evans Memorial, Massachusetts Memorial Hospitals and Harvard University School of Business Administration*  
Variations in visual thresholds during carbon monoxide and hypoxic anoxia

- 12 Charles Haig and Samuel L Saltzman (*by invitation*), *New York Medical College*  
Retinal sensitivity contours in retinitis pigmentosa I Sensitivity to white light
- 13 Charlotte M Sullivan (*by invitation*) and Kenneth C Fisher, *University of Toronto*  
Temperature selection and the effects of light and temperature on movements in fish
- 14 Leon H Schneyer (*introduced by* A M Shanes), *Marine Biological Laboratory and New York University College of Dentistry*  
A temperature potassium antagonism observed in luminous bacteria

## PHYSIOLOGY B

Monday, 9 00 a m

GRAND BALLROOM, STEVENS HOTEL

## Hypertension

- 1 Eleanore Tripp (*by invitation*) and Eric Ogden, *University of Texas School of Medicine*  
Pressor substances in dog plasma incubated with renin
- 2 Maurice M Rapport (*by invitation*), Arda Alden Green (*by invitation*) and Irvine H Page, *Cleveland Clinic Foundation*  
Purification of the substance which is responsible for the vasoconstrictor activity of serum
- 3 R E Shipley, O M Helmer (*by invitation*) and K G Kohlstaedt (*by invitation*), *Indianapolis City Hospital*  
Presence in blood of a principle which elicits a sustained pressor response in nephrectomized animals
- 4 O M Helmer (*by invitation*), R E Shipley and K G Kohlstaedt (*by invitation*), *Indianapolis City Hospital*  
Nature of a principle in blood which elicits a sustained pressor response in nephrectomized animals
- 5 Dean A Collins, *University of Illinois and Temple University*  
Preliminary studies of the assay of hypertensin (Angiotonin)
- 6 F J Kottke and W G Kubicek (*introduced by* M B Visseher), *University of Minnesota Medical School*  
Renal Plasma flow and glomerular filtration in the dog in relation to arterial hypertension and renal damage
- 7 J Leal Prado (*by invitation*), Paul Dontigny (*by invitation*), Eleanor Hav and Hans Selve, *Universite de Montreal*  
Further studies concerning the role of the diet



in the production of nephrosclerosis and hypertension by anterior pituitary preparations

- 8 **G E Wakerlin, Wayne Donaldson** (*by invitation*), **Oliver Kamm** (*by invitation*), **H Minatoya** (*by invitation*), **T Lefco** (*by invitation*), and **John Marshall** (*by invitation*), *University of Illinois College of Medicine, and Parke, Davis and Co Research Laboratories*

Further studies on the treatment of experimental renal hypertension with renal extract fractions

- 9 **E A Ohler** (*by invitation*) and **G E Wakerlin**, *University of Illinois College of Medicine*  
Treatment of experimental renal hypertension with pargidine hydrobromides
- 10 **A Suritskin** (*by invitation*), **M Wilburne** (*by invitation*) and **S Rodbard**, *Michael Reese Hospital*

The action of dibenamine (Dibenzyl-Beta-Chloroethyl Amine) in experimental hypertension

- 11 **W G Moss** (*by invitation*) and **G E Wakerlin**, *University of Illinois College of Medicine*  
Role of the nervous system in early and late hypertension in the dog
- 12 **Edmund Jacobson**, *Laboratory for Clinical Physiology, Chicago*  
The influence of relaxation upon the blood pressure in "essential hypertension"

- 13 **L N Katz, M Wilburne** (*by invitation*) and **S Rodbard**, *Michael Reese Hospital*  
The effect of hypertension on the blood pressure responses to epinephrine and pentobarbital

- 14 **Ephraim Shorr, B W Zweifach, R F Furchgott** (*by invitation*) and **S Baez** (*by invitation*), *Cornell University Medical College and the New York Hospital*

Hepato renal factors in circulatory homeostasis XII Alterations in renal vaso-ejector mechanisms during experimental hypertension

- 15 **B W Zweifach, S Baez** (*by invitation*) and **Ephraim Shorr**, *Cornell University Medical College and the New York Hospital*

Hepato renal factors in circulatory homeostasis XIII Effects of acute renal ischemia on the renal vaso-ejector mechanisms

- 16 **S Baez** (*by invitation*), **B W Zweifach** and **Ephraim Shorr**, *Cornell University Medical College and the New York Hospital*

Hepato Renal factors in circulatory homeostasis XIV Vascular effects of acute renal occlusion in dogs

## PHYSIOLOGY C

Monday, 9 00 a m

NORTH BALLROOM, STEVENS HOTEL

### Cerebral Cortex

- 1 **Virginia D Davenport** (*by invitation*), **Horace W Davenport**, and **Lowell A Woodbury** (*by invitation*), *University of Utah School of Medicine*

Cortical excitability in pyridoxine-deficient rats

- 2 **Ralph W Wager** (*introduced by Theodore G Bernthal*), *Medical College of the State of South Carolina*

On the role of glutamic acid in epilepsy

- 3 **Jane Hyde** (*by invitation*), **Sibyl Beckett** (*by invitation*) and **Ernst Gellhorn**, *University of Minnesota Medical School*

Acetylcholine, cholinesterase, eserine and convulsions

- 4 **Lowell A Woodbury** and **C A Swinyard** (*introduced by James E P Toman*), *University of Utah School of Medicine*

Energy requirements for the electrical production of seizures

- 5 **Willem F Kremer** (*introduced by C L Gemmill*), *University of Virginia Medical School*  
Blood pressure changes in response to electrical and chemical stimulation of the cerebral cortex

- 6 **M D Wheatley** (*by invitation*) and **W S McCulloch**, *University of Illinois College of Medicine*

Sundry changes in physiology of cerebral cortex following rapid injection of sodium cyanide

- 7 **H T Chang** (*by invitation*), **C N Woolsey**, **L W Jarcho** (*by invitation*) and **E Henne-man** (*by invitation*), *Johns Hopkins University*

Representation of cutaneous tactile sensibility in the cerebral cortex of the spider monkey

- 8 **O Sugar, J D French** and **J Chusid** (*introduced by Warren S McCulloch*), *University of Illinois College of Medicine and Illinois Neuropsychiatric Institute*

Corticocortical connections of the superior surface of the temporal operculum in the macaque (*macaca mulatta*)

- 9 **J D French, O Sugar** and **J Chusid** (*introduced by Warren S McCulloch*), *University of Illinois College of Medicine and the Illinois Neuropsychiatric Institute*

Cortical connections of parietal and frontal opercula in the monkey (*macaca mulatta*)

- 10 **J M R Delgado** (*by invitation*), **J F Fulton** and **R B Livingston** (*by invitation*), *Yale University School of Medicine*

- Stimulation of area 13 and skin temperature changes following its ablation
- 11 J F Fulton, R B Livingston (*by invitation*) and G D Davis (*by invitation*), *Yale University School of Medicine*  
Ablation of area 13 in primates
  - 12 Wilbur K Smith, *The University of Rochester School of Medicine & Dentistry*,  
The relation of cytoarchitecture to response elicited by electrical excitation of the cerebral cortex
  - 13 Virginia L Otterback (*by invitation*) and W Horsley Gantt, *Paulownia Laboratory of the Phipps Psychiatric Clinic, Johns Hopkins University*  
Latent period as an index of intensity of the conditional reflex
  - 14 William F Allen, *University of Oregon Medical School*  
Effect of three bilateral cerebral lesions on correct cutaneous conditioned differential responses of dog's foreleg
  - 15 Reg B Bromley (*introduced by Philip Bard*), *Johns Hopkins University*  
Relation of areas of cortical ablation to the leg responding to a conditioned stimulus

## PHYSIOLOGY D

Monday, 9 00 a m

PARLORS ABC, CONGRESS HOTEL

## Gastric Secretion

- 1 Harry Shay, S A Komarov and Margot Gruenstein (*by invitation*), *Temple University School of Medicine*  
Studies on the effects of vagotomy in rats
- 2 Henry N Harkins and Stuart R Elliott, II (*by invitation*), *Johns Hopkins University*  
The influence of vagotomy on ulceration of the gastric rumen of rats following pyloric ligation
- 3 G A Hallenbeck, Charles F Code and R A Gregory (*by invitation*), *Mayo Foundation*  
The histamine content of gastric juice
- 4 Lester R Dragstedt, E Bruce Tovee (*by invitation*), Edward R Woodward (*by invitation*), and Paul V Harper (*by invitation*), *University of Chicago*  
The relative importance of nervous and humoral factors in gastric secretion
- 5 Julius Wenger (*by invitation*) and Harry Greengard, *Northwestern University Medical School*  
The pepsinogogue effect of a pancreozymin concentrate
- 6 Frank E Visscher and Donald R Rayman (*introduced by D J Ingle*), *The Upjohn Co*  
Effect of enterogastrone on gastric secretion of pyloric ligated rats
- 7 Arne N Wick (*by invitation*), Frances Pauls (*by invitation*), Alice Jean Irish (*by invitation*) and Eaton M MacKay, *Scripps Metabolic Clinic, La Jolla, Calif*  
Comparison of the anti ulcer activity of enterogastrone and urinary antihelones
- 8 Jesse N Frederick (*by invitation*) and Harry Greengard, *Northwestern University Medical School*  
A method for determining the ulcer preventive factor in enterogastrone concentrates
- 9 E A Risley (*by invitation*), W B Raymond (*by invitation*) and R H Barnes, *Medical Research Division, Sharp & Dohme, Inc*  
The use of the Shay rat in studying anti ulcer substances (Biochem )
- 10 G M Cummins (*by invitation*), M I Grossman, and A C Ivy, *Northwestern University Medical School*  
The acid factor in the production of gastrointestinal ulcers in dogs
- 11 T L Patterson, J Kaulbersz, D J Sandweiss and H C Saltzstein (*by invitation*), *Wayne University College of Medicine and Harper Hospital*  
Different periods of administration of enterogastrone and urogastrone in double histamine experiments
- 12 J Kaulbersz, T L Patterson, D J Sandweiss and H C Saltzstein (*by invitation*), *Wayne University College of Medicine and Harper Hospital*  
Urine extracts of hypophysectomized dogs administered in different periods of a double histamine experiment
- 13 M I Grossman, R Villarreal (*by invitation*), G Westphal (*by invitation*) and A C Ivy, *Northwestern University Medical School*  
Acceleration of the rate of healing of surgically excised gastric mucosal defects by "enterogastrone" administration
- 14 S A Komarov, Herman Siplet (*by invitation*) and Harry Shay, *Fels Research Institute, Temple University School of Medicine*  
Gastric mucin A new quantitative method for its determination Secretion of mucin under various conditions
- 15 B P Sonnenblick (*by invitation*), Herbert A Sober (*by invitation*) and Franklin Hollander, *The Mount Sinai Hospital, New York City*  
Influence of repeated eugenol stimulation on the gastric mucosa as studied in mucus smears (Biochem )
- 16 Herbert A Sober (*by invitation*), B P Sonnenblick (*by invitation*) and Franklin Hol-

lander, *The Mount Sinai Hospital, New York City*

Response of the Heidenhain pouch to repeated application of eugenol (Biochem)

### PHYSIOLOGY E

Monday, 9 00 a m

ROOM 12, STEVENS HOTEL

#### Teaching and Research Methods

- 1 W A Selle, *University of Texas Medical Branch*

Returns of questionnaire concerning biophysics sent to deans and physiologists of American Medical Schools

- 2 Frederic T Jung and Lillian E Cisler (*by invitation*), *Northwestern University Medical School*

The relation of measurement of enthusiasm-staleness to measurements of physical-fitness, for medical students under the accelerated program

- 3 Frank R Blood (*by invitation*) and Fred E D'Amour, *University of Denver*

Suitability of the rat for routine laboratory work in physiology

- 4 Kenneth E Jochim and John F McDonnell (*by invitation*), *University of Kansas*

Factors influencing pulse volume in models of the circulatory system

- 5 Robert K Spiro, Robert S Aaron and John S Thompson (*introduced by J Raymond Johnson*), *Long Island College of Medicine*

Experiments on the live rocking method of artificial resuscitation

- 6 Paul L McLain (*introduced by C C Guthrie*), *University of Pittsburgh*

Comparison of centrifugal hematoerit techniques

- 7 A K Davis (*by invitation*) and Richard R Overman, *University of Tennessee College of Medicine*

The application of flame photometry to sodium and potassium determinations in biological fluids

- 8 L H Peterson (*introduced by H C Bazett*), *University of Pennsylvania Medical School*

A method for introduction and use of a flexible plastic arterial catheter of small diameter

- 9 C H William Ruhe (*introduced by C C Guthrie*) *University of Pittsburgh*

A method for the preparation of crystallized oxyhemoglobin

### JOINT SESSION OF THE FEDERATION

Monday, 1 45 p m

GRAND BALLROOM, STEVENS HOTEL

Program on p 3

### PHYSIOLOGY BUSINESS MEETING

Monday, 4 15 p m

NORTH BALLROOM, STEVENS HOTEL

#### Special Meeting

### REPORT OF THE COMMITTEE ON TEACHING PROBLEMS IN PHYSIOLOGY

A SIMPOSIUM—DISCUSSION

Monday, 8 00 p m

GRAND BALLROOM, STEVENS HOTEL

#### Perspectives in Physiological Education Wallace O Fenn, Chairman

- 1 Paul Weiss, *University of Chicago*  
The Place of Physiology in the Biological Sciences
- 2 Eugene M Landis, *Harvard University*  
The Interdependence of Physiology and Medicine
- 3 Laurence Irving, *Swarthmore College*  
Zoophysiology
- 4 Ralph W Gerard, *University of Chicago*  
The Task of the American Physiological Society

Full discussion will be invited after the presentation of these statements. An informal opinion poll may be taken

### PHYSIOLOGY A

Tuesday, 9 00 a m

GRAND BALLROOM, STEVENS HOTEL

#### Symposium

### Functional Organization of the Cerebral Cortex Philip Bard, Chairman

- 1 Clinton N Woolsey, *Johns Hopkins University*  
Patterns of sensory representation
- 2 Marion Hines, *Johns Hopkins University*  
Functional organization of cortical motor mechanisms
- 3 Warren S McCulloch, *University of Illinois*  
Intracortical organization
- 4 Theodore B Rasmussen, *Montreal Neurological Institute*  
Functional organization of sensory and motor areas in man

Discussion will follow the presentation of all four papers

## PHYSIOLOGY B

Tuesday, 9 00 a m

PINE ROOM, CONGRESS HOTEL

## Body Fluids

- 1 Philip Dow, *University of Georgia School of Medicine*  
Binding of brilliant vital red and T-1824 by serum albumin comparative spectrophotometric studies
- 2 Hampden C Lawson and David T Overbey (by invitation), *University of Louisville School of Medicine*  
The mixing of dye and of red cells in the cardiovascular system
- 3 Thomas H Allen (introduced by Magnus I Grogersen), *College of Physicians and Surgeons*  
Dissociation of T-1824 albumin by synthetic detergent
- 4 Frank Gollan (introduced by M B Visseher), *University of Minnesota Medical School*  
The relation between plasma protein concentration and T 1824 disappearance rate in plasma volume determination
- 5 A T Miller, Jr, *University of North Carolina Medical School*  
The excretion of the blue dye T 1824 in the bile
- 6 Jack P Saunders, Richard G Horton and Raymond E Weston (introduced by Harold E Himwich), *Edgewood Arsenal Medical Division*  
Blood volume in the dog determined by Evans blue and Cyanide disappearance
- 7 Arthur W Martin, *University of Washington*  
The blood volume of some elasmobranchs
- 8 C R Spealman, M Newton (by invitation) and R L Post (by invitation), *University of Pennsylvania*  
The ratio between total circulating hemoglobin and total plasma protein
- 9 Austin Henschel, Henry Longstreet Taylor, Ansel Keys and Angie Mae Sturgeon (by invitation), *University of Minnesota*  
Blood and plasma changes in semi starvation and subsequent rehabilitation
- 10 Ansel Keys, Joseph Brozek (by invitation), Olaf Mickelsen (by invitation), Austin Henschel and Henry Longstreet Taylor, *University of Minnesota*  
Total body fluid, fat, and active tissue in starvation and subsequent rehabilitation
- 11 A V Wolf, D E Lester (by invitation), L W Gorham (by invitation) and H H Shultz (by invitation), *Albany Medical College and Albany Hospital*

The relative importance of dietary sodium chloride and water in cardiac edema

- 12 A Soto-Rivera (by invitation) and J R Pappenheimer, *Harvard Medical School*  
The effective osmotic pressure of the plasma proteins in mammalian capillaries
- 13 Frank Folk (by invitation), C I Reed, and N R Joseph (by invitation), *University of Illinois*  
The response of the pH of synovial fluid in the anesthetized dog to circulatory influence
- 14 I E Steck (by invitation), N R Joseph (by invitation), and C I Reed, *University of Illinois*  
The pH of synovial fluid in the anaesthetized dog under treatment with metrazol and insulin
- 15 N R Joseph (by invitation), Harvey Horwitz (by invitation), and C I Reed, *University of Illinois*  
Observations on the chemistry of synovial fluid in human subjects

## PHYSIOLOGY C

Tuesday, 9 00 a m

PARLORS ABC, CONGRESS HOTEL

## Metabolism

- 1 J R Brobeck, *Yale University School of Medicine*  
Regulations of energy exchange in rats
- 2 Nathan W Shock, *National Institute of Health and Baltimore City Hospitals*  
The acid base balance of the blood of aged males
- 3 A J Steigman (by invitation), A Sokalchuk (by invitation), D Ellis (by invitation), and E M Greisheimer, *Temple University School of Medicine*  
Some effects of cytochrome C on the oxygen economy of anesthetized dogs
- 4 Sidney Roberts and Clara M Szego, *Worcester Foundation for Experimental Biology*  
The influence of fasting on the peripheral utilization of sodium beta hydroxybutyrate in the rat
- 5 Samuel R Tipton, *Medical College of Alabama*  
The effect of diet on respiration and respiratory enzymes of liver from hyperthyroid rats
- 6 Horace W Davenport, *University of Utah School of Medicine*  
The oxidative metabolism of the mouse stomach
- 7 W A Himwich and J P Saunders (introduced by Harold E Himwich) *Edgewood Arsenal*  
The conversion of cyanide to thiocyanate by tissues

- 8 Alfred Marshak, *Tuberculosis Control Division, U S Public Health Service*  
Nucleoproteins of rat liver nuclei
- 9 William Montagna (by invitation) and James B Hamilton, *Long Island College of Medicine*  
Histochemical analysis of the sebaceous glands of the hamster
- 10 Willie W Smith, *National Institute of Health*  
The relationship between protein and the sulfur-containing amino acids in protection against methyl chloride poisoning
- 11 Charles D Kochakian, Jean G Moe (by invitation), M Lucile Hunter (by invitation), and Constance E Stettner (by invitation), *University of Rochester*  
The protein anabolic property of testosterone propionate in normal, castrated, adrenalectomized and hypophysectomized rats
- 12 Hans Selye and Helen Stone (by invitation), *Universite de Montreal*  
Effect of methyl-testosterone upon the "endocrine kidney"
- 13 William B Langan (introduced by Charles Haig), *New York Medical College*  
Steroid depression in *Rana pipiens*
- 14 Gregory Pincus, *Worcester Foundation for Experimental Biology*  
Estrone oxidation products A comparative study of estrone, marrianolic acid and estrollic acid
- 5 Samuel A Corson, Elinor Foster (by invitation), Elizabeth Radway (by invitation) and James O Elam (by invitation), *University of Minnesota Medical School*  
The mechanism of diuretic action of salts of organic acids
- 6 J Maxwell Little, *The Bowman Gray School of Medicine of Wake Forest College*  
Diuresis in unanesthetized dogs following the intravenous injection of dog, human, or dialyzed human urine
- 7 George Pallade (introduced by Robert Chambers), *Washington Square College*  
Urea secretion of chick mesonephric tubules in tissue culture
- 8 Ingrid J Deyrup (introduced by Magnus I Gregersen), *College of Physicians and Surgeons, Columbia University*  
The effect of posture on the creatinine clearance of unanesthetized dogs
- 9 Lemuel D Wright (by invitation), Horace F Russo (by invitation), Helen R Skeggs (by invitation), Grace A Shaner (by invitation) and Karl H Beyer, *Sharp & Dohme, Medical Research Division*  
The renal clearance of essential amino acids
- 10 A C Corcoran and Irvine H Page (with the assistance of A Buckingham), *Cleveland Clinic Foundation*  
Effect on renal function of rats of substances containing vitamin A
- 11 Alan C Burton and R Gunton (by invitation), *University of Western Ontario*  
The concentration of protein in normal urine, measured by its surface activity
- 12 William H Olson, Ethel Carter (by invitation) and H Necheles, *Michael Reese Hospital*  
Studies of hemoglobinemia and its effect on kidney excretion
- 13 Eric Ogden, *University of Texas School of Medicine*  
Total body water as related to urea elimination
- 14 E F Adolph, *University of Rochester*  
Forced water drinking

### PHYSIOLOGY A

Tuesday, 2 00 p m

LOWER TOWER ROOM, STEVENS HOTEL

#### General Physiology—Renal Function

- 1 W D Lotspeich (introduced by R F Pitts), *Syracuse University College of Medicine*  
The renal reabsorption and excretion of inorganic sulfate
- 2 J L Ayer (by invitation), W A Schiess (by invitation) and R F Pitts, *Syracuse University College of Medicine*  
The relationship between the renal tubular reabsorptive capacity for phosphate and glomerular filtration rate
- 3 W A Schiess (by invitation), J L Ayer (by invitation), W D Lotspeich (by invitation) and R F Pitts, *Syracuse University College of Medicine*  
Factors determining the rate of acid excretion by the normal human kidney
- 4 R F Pitts, W D Lotspeich (by invitation), J L Ayer (by invitation) and W A Schiess (by invitation), *Syracuse University College of Medicine*  
The nature of the human renal mechanism for acidifying the urine

### PHYSIOLOGY B

Tuesday, 2 00 p m

NORTH BALLROOM, STEVENS HOTEL

#### Cardiac Output and Peripheral Circulation

- 1 H L White, *Washington University School of Medicine*  
Electrical conductivity method for cardiac output
- 2 John L Nickerson, *College of Physicians and Surgeons*  
The interpretation of the ballistocardiograph pattern

- 3 John W Remington and W F Hamilton,  
*University of Georgia School of Medicine*  
The relation between the duration of systole,  
stroke volume, ventricular work and cycle  
length
- 4 Hurley L Motley (by invitation), Lars Werko  
(by invitation) and Andre Cournand, *College  
of Physicians and Surgeons, Columbia Uni-  
versity*  
Influence of intermittent positive pressure  
breathing on cardiac output
- 5 Andre Cournand, Hurley L Motley (by in-  
vitation), and Lars Werko (by invitation),  
*College of Physicians and Surgeons, Columbia  
University*  
Mechanism underlying cardiac output change  
during intermittent positive pressure breath-  
ing (IPP)
- 6 David M French, Walter M Booker and  
Pedro A Molano (introduced by Dr A B  
Luckhardt), *Howard University School of  
Medicine*  
Acute and chronic studies in abdominal dis-  
tention
- 7 Irwin H Slater and Harry F Weisberg (in-  
troduced by Richard C de Bodo), *New York  
University College of Medicine*  
The role of the pericardium in acute cardiac  
dilatation
- 8 H D Bruner, John K Clark (by invitation)  
and Harold G Barker (by invitation),  
*University of Pennsylvania*  
Circulation time through the kidney
- 9 W W Walcott and F Velasquez (introduced  
by Magnus I Gregersen), *College of Physi-  
cians and Surgeons, Columbia University*  
Determination of regional blood flow
- 10 M Wilburne, J Schlichter, M Grossman and  
F Cisneros (introduced by L N Katz),  
*Michael Reese Hospital*  
Acetylcholine in the objective determination  
of circulation time
- 11 J V Warren (by invitation) and E A Stead,  
Jr, *Yale and Duke Medical Schools*  
Control of the cardiac output in man Studies  
on reactive hyperemia
- 12 Campbell Moses (introduced by C C Guthrie),  
*University of Pittsburgh*  
An experimental study of intramascular pres-  
sure measurements
- 13 Seymour S Kety (by invitation), Merel H  
Harmel (by invitation), Henry A Shenkin  
(by invitation) and Carl F Schmidt, *Uni-  
versity of Pennsylvania*  
Nitrous Oxide method for measurement of  
human cerebral blood flow Experimental  
evaluation of fundamental assumptions

## PHYSIOLOGY C

Tuesday, 2 00 p m

UPPER TOWER ROOM, STEVENS HOTEL

## Central Nervous System

- 1 L F Nims and F E Nulsen (by invitation),  
*Yale University School of Medicine*  
Interaction of cerebral cortex and cerebellum
- 2 V Soriano (by invitation) and J F Fulton,  
*Yale University School of Medicine*  
Interrelation between anterior lobe of the  
cerebellum and the motor area
- 3 Joseph E Hawkins, Jr, *Merck Institute for  
Therapeutic Research*  
Disturbances of vestibular function produced  
in animals by streptomycin
- 4 L M N Bach (by invitation) and H W  
Magoun, *Northwestern University Medical  
School*  
The vestibular nuclei as an excitatory mecha-  
nism for the cord
- 5 W H Sweet (by invitation), W S McCulloch  
and R S Snider (by invitation), *University  
of Illinois College of Medicine and North-  
western University School of Medicine*  
Repetitive movements on basal ganglia stimu-  
lation after transection of cerebral peduncles
- 6 Robert G Heath (by invitation), David A  
Freedman (by invitation) and Fred A Mett-  
ler, *College of Physicians and Surgeons,  
Columbia University*  
Striatal removal without previous cortical  
ablation, release, disorientation, metabolic  
disturbance
- 7 Jerzy E Rose (by invitation), Clinton N  
Woolsey, and Leonard W Jarecho (by invita-  
tion), *Johns Hopkins University*  
Relations of anterior thalamic nuclei and mam-  
millothalamic tract to limbic cortex
- 8 Berry Campbell, *University of Minnesota  
Medical School*  
The electroarchitectonic map of the anti-  
dromic potential
- 9 Clinton N Woolsey and Hsiang-Tung Chang  
(by invitation), *Johns Hopkins University*  
Cortical origin of the pyramidal tract as  
defined by antidromic volleys from the medul-  
lary pyramid
- 10 R S Snider (by invitation), H W Magoun  
and W S McCulloch, *University of Illinois  
College of Medicine and Northwestern Uni-  
versity School of Medicine*  
A suppressor cerebello bulbo reticular pathway  
from anterior lobe and paramedian lobules
- 11 G N Loofbourrow (introduced by E Gell-  
horn), *University of Minnesota*

Relation of electrogram to mechanogram in mammalian skeletal muscle in different conditions

- 12 A A Ward, Jr (*by invitation*), W S McCulloch and H W Magoun, *University of Illinois College of Medicine and Northwestern University Medical School*

Production of tremor at rest in the monkey

- 13 Chester W Darrow and Charles E Henry (*by invitation*), *Institute for Juvenile Research*  
A basis for interpreting autonomic-EEG relationships

- 14 Charles E Henry (*by invitation*) and Chester W Darrow, *Institute for Juvenile Research*  
Autonomic factors in the relation of EEG to heart rate

- 15 B S Lipton (*by invitation*) and F A Gibbs, *University of Illinois College of Medicine*  
Changes in the human electroencephalogram produced by sodium cyanide

#### PHYSIOLOGY D

Tuesday, 2 00 p m

WEST BALLROOM, STEVENS HOTEL

##### Performance

- 1 David B Tyler, *California Institute of Technology*  
The "fatigue" of prolonged wakefulness
- 2 John Haldi, Winfrey Wynn (*by invitation*) and Charles Ensor (*by invitation*), *Emory University*  
The effect of sugar and other food materials on the increased spontaneous activity induced by caffeine
- 3 D M Green (*introduced by* R Frederick Becker), *University of Washington*  
Anoxic variations in human performance  
Sid Robinson, *Indiana University*  
The control of sweating in working man
- 5 Steven M Horvath, A Friedman (*by invitation*) and H Golden (*by invitation*), *Armored Medical Research Laboratory*  
Acclimatization to extreme cold
- 6 Robert E Johnson and R M Kark (*by invitation*), *U S Army Medical Nutrition Laboratory*  
Environment and caloric requirements
- 7 R F Dern (*introduced by* W O Fenn), *University of Rochester School of Medicine and Dentistry*  
Velocity of arm flexions under varying loads
- 8 F A Hellebrandt, Sara Jane Houtz (*by invitation*) and Ellen Neall Duvall (*by invitation*), *Medical College of Virginia*  
The influence of mecholy and histamine iontophoresis on recovery from fatigue

- 9 Marjorie Wilson (*by invitation*), W W Tuttle and Kate Daum (*by invitation*), *State University of Iowa*

The effect of low thiamine intake on the oxygen required by women to perform work

- 10 V E Hall, E Munoz (*by invitation*), and B Fitch (*by invitation*), *Stanford University*  
Reduction of the amplitude of muscle contraction by application of moist heat to overlying skin

- 11 Ernst Simonson, Josef Brozek (*by invitation*) and Ancel Keys, *University of Minnesota*  
Effect of three types of illuminants on visual performance and fatigue

- 12 Josef Brozek (*by invitation*), Ernst Simonson and Ancel Keys, *University of Minnesota*  
Changes in visual functions and performance after 2 hours of intensive inspection work at 2 footcandles

- 13 Clara Torda and Harold G Wolff, *New York Hospital and Cornell University Medical College*

Effect of amino acids on muscle function of patients with myasthenia gravis

#### PHYSIOLOGY E

Tuesday, 2 00 p m

PRIVATE DINING ROOM 2, STEVENS HOTEL

##### Reproduction

- 1 Carl G Heller, Warren O Nelson and (*by invitation*) Edwin C Jungck and William O Maddock, *University of Oregon Medical School and University of Iowa Medical School*  
Correlation of urinary gonadotrophin titers with degree of seminiferous tubule involvement in human male sterility
- 2 Edwin C Jungck (*by invitation*), W O Maddock (*by invitation*), J T Van Bruggen (*by invitation*) and Carl G Heller, *University of Oregon Medical School*  
Blood vitamins A, C and E and seminal fluid vitamin C in human male sterility
- 3 George Clark, *Yerkes Laboratories of Primate Biology and Yale University*  
Threshold bleeding and the sex skin in the castrate female chimpanzee
- 4 F A Gassner and Bernard B Longwell (*introduced by* C A Maaske), *Colorado Agricultural Experiment Station and University of Colorado School of Medicine*  
Fecal excretion of androgens by the dairy cow during pregnancy
- 5 Betty Blaylock (*by invitation*) and Frederick E Emery, *University of Arkansas*  
Action of prostigmine methylsulphate on the reproductive organs of rats

- 6 Clara M Szego and Sidney Roberts, *Worcester Foundation for Experimental Biology*  
Blood estrogen levels during human pregnancy
- 7 Warren O Nelson and Carl G Heller, *State University of Iowa and College of Medicine, University of Oregon*  
Primary and Secondary failure of the human testis
- 8 Irving Rothchild and R M Fraps (introduced by Rachmiel Levine), *U S Department of Agriculture*  
The release of ovulating hormone from the hen's pituitary by means of progesterone
- 9 Brooks Ranney (by invitation), B M Peckham (by invitation) and R R Greene, *Northwestern University Medical School*  
Non-effect of hysterectomy on the ovary
- 10 William T Salter, Frances D Humm (by invitation) and M Jane Oesterling (by invitation), *Yale University School of Medicine*  
The antithetical ratio for urinary steroids in various pathologic and physiologic conditions
- 11 Harry B Friedgood and Josephine B Garst (by invitation), *Cancer Research Foundation of California, and California Institute of Technology*  
Assay of urinary estrogens by ultraviolet absorption spectrophotometry
- 12 H S Guterman and M S Schroeder (introduced by R Levine), *Michael Reese Hospital*  
A simplified technique for the quantitative colorimetric estimation of pregnandiol in urine
- 13 B M Peckham (by invitation) and R R Greene, *Northwestern University Medical School*  
Successful production of secondary deciduomata
- 14 Charles F Morgan (introduced by T Koppanyi), *Georgetown University School of Medicine*  
Reproductive tract modification in the female opossum during and following exposure to light
- 15 W T Pommerenke (introduced by Dr Wallace O Fenn), *University of Rochester School of Medicine and Dentistry*  
Cyclic variations in the concentration of copper reducing substances in cervical secretions

#### PHYSIOLOGY EDITORIAL CONFERENCE

Tuesday 7 30 p m

ROOM 13, STEVENS HOTEL

A C Ivy, Chairman

Members interested in publication affairs are cordially invited to attend

#### PHYSIOLOGY A

Wednesday, 9 00 a m

NORTH BALLROOM, STEVENS HOTEL

#### General Physiology—Junctional Transmission

- 1 Robert Hodes, *University of Pennsylvania*  
The electrical activity of single motor units in human poliomyelitis
- 2 Herbert H Jasper, *McGill University and the Montreal Neurological Institute*  
Integration and disintegration of motor units, unipolar electromyography in neuro-muscular diseases
- 3 James E P Toman, J Walter Woodbury (by invitation), and Lowell A Woodbury (by invitation), *University of Utah School of Medicine*  
Nerve conduction block by di isopropyl fluorophosphate (DFP) and eserine without change in demarcation potential
- 4 J Walter Woodbury (by invitation), Lowell A Woodbury (by invitation), and James E P Toman, *University of Utah*  
Some effects of di-isopropyl fluorophosphate (DFP) and fluoride ion on frog sciatic nerve
- 5 Kenneth D Roeder and Nancy K Kennedy (by invitation), *Tufts College*  
Action of anticholinesterases on axones and synapses in the cockroach (*Periplaneta americana*)
- 6 David Nachmansohn and Mortimer A Rothenberg (by invitation), *Columbia University College of Physicians and Surgeons*  
Effect of anticholinesterases on conduction of nerve and muscle
- 7 John C Finerty (introduced by Robert Gesell), *University of Michigan*  
Potentiation of response of rectus abdominis of frog to acetylcholine by diisopropyl fluorophosphate
- 8 Charles R Brassfield, Clance Biggins (by invitation), and Merle M Musselman (by invitation), *University of Michigan*  
The effects of diisopropyl-fluorophosphate upon the submaxillary gland
- 9 Charles R Lowe (introduced by Robert Gesell), *University of Michigan*  
On some physiological effects of anticholinesterases
- 10 Saul L Cohen (introduced by Robert Gesell), *University of Michigan*  
The effect of diisopropyl-fluorophosphate upon the response of the turtle heart to vagus stimulation
- 11 Jeane Siskel Frey (by invitation) and Robert Gesell, *University of Michigan*  
Further study of central chemical control of breathing with aid of diisopropyl fluorophosphate and prostigmine



- 12 Richard H Lillie (*by invitation*) and Robert Gesell, *University of Michigan*  
Comparison of rhythmic movements of breathing and progression Evidence for common mechanisms

### PHYSIOLOGY B

Wednesday 9 00 a m

GRAND BALLROOM, STEVENS HOTEL

#### Regulation of Circulation

- 1 J B Nolasco and R Kohrman (*introduced by C J Wiggers*), *Western Reserve University School of Medicine*  
The cardiovascular effects of afferent stimulation of the phrenic nerves
- 2 S C Wang and Herbert L Borison (*by invitation*), *College of Physicians and Surgeons, Columbia University*  
An analysis of the carotid sinus cardiovascular mechanism
- 3 A Leimdorfer (*introduced by W S McCulloch*), *University of Illinois College of Medicine*  
A pulmonary cardiovascular reflex in man
- 4 W B Youmans, H V Good (*by invitation*), and A F Hewitt (*by invitation*), *University of Oregon Medical School*  
Regulation of heart rate after chronic sino-aortic denervation
- 5 Chentze Hsiang Wu (*by invitation*) and M B Visscher, *University of Minnesota Medical School*  
Measurements of blood pressure in the mouse with special reference to age  
W F Hamilton and John W Remington, *University of Georgia School of Medicine*  
Some immediate responses to a sudden reduction in peripheral resistance
- 7 Norman C Wheeler (*by invitation*), John W Remington and W F Hamilton, *University of Georgia School of Medicine*  
Some immediate responses involved in increased arterial pressure
- 8 Harold M Peck (*introduced by Karl H Beyer*), *Western Reserve University, and Medical Research Division, Sharp & Dohme, Inc*  
Effect of environmental temperature changes on the living white mouse spleen
- 9 W F Greenwood, J R DiPalma and J Stokes, III (*introduced by E M Landis*), *Harvard Medical School*  
Factors affecting the appearance and persistence of visible cutaneous reactive hyperemia in man
- 10 A C Barger and L H Smith, Jr (*introduced by L M Landis*), *Harvard Medical School*  
Venous pressure and cutaneous reactive hy-

peremia in exercise and other circulatory stresses

- 11 A B Hertzman and W C Randall, *St Louis University School of Medicine*  
Estimation of cutaneous blood flow with the photoelectric plethysmograph in the presence of arterial pathology
- 12 F E Franke, W C Randall, D E Smith (*by invitation*), and A B Hertzman, *St Louis University School of Medicine*  
Vasomotor and sudomotor patterns in the skin of the finger and forearm
- 13 R T Martin (*by invitation*), A B Hertzman and W C Randall, *St Louis University School of Medicine*  
Arterial pressure gradients, arterial oscillometry and cutaneous blood flow in the analysis of arterial obstruction
- 14 Grace M Roth and Charles Sheard, *Mayo Clinic and Mayo Foundation*  
Maintenance of vasodilatation of the extremities of normal persons over a prolonged period after successive meals
- 15 John F Perkins, Jr and Mao-Chih Li (*introduced by E M Landis*), *Harvard Medical School*  
A sudden fall in the skin temperature of denervated or sympathectomized paws exposed to cold
- 16 B G Ferris, Jr, R E Forster, II, E L Pillion and W R Christensen (*introduced by H S Belding*), *Climatic Research Laboratory*  
Control of peripheral blood flow Responses in the human hand when other extremities are warmed

### PHYSIOLOGY C

Wednesday 9 00 a m

NORTH ASSEMBLY ROOM, STEVENS HOTEL

#### Aviation Physiology

- 1 E L Corey, *University of Virginia*  
Tests on explosive decompression
- 2 Fred A Hitchcock and Abraham Edelmann (*by invitation*), *Ohio State University*  
The response of normal dogs to explosive decompression to 30 mm of Hg
- 3 Abraham Edelmann and R W Stacy (*introduced by Fred A Hitchcock*), *Ohio State University*  
The effect of explosive decompression to 30 mm Hg on the lung volume of the rat
- 4 R B Livingston (*by invitation*), S Gelfand and L F Nims, *Yale University School of Medicine*  
Pathology in suddenly decompressed rats
- 5 S Gelfand, L F Nims and R B Livingston (*by invitation*), *Yale University School of Medicine*

- Cause of death from explosive decompression at high altitudes
- 6 H E Savely (*by invitation*), W H Ames, 1st Lt, M C (*by invitation*), and H M Sweeney, *Wright Field*  
Some factors in ejection of personnel from high speed aircraft
- 7 John W Bean, *University of Michigan Medical School*  
Changes in arterial pH induced by compression and decompression
- 8 Douglas W Lund, Capt, M C (*introduced by* H M Sweeney), *Wright Field*  
Man's tolerance to positive acceleration in different orientations of the body
- 9 James L Gamble, 1st Lt, M C and Robert S Shaw, 1st Lt, M C (*introduced by* H M Sweeney), *Wright Field*  
Preliminary observations on dogs subjected to negative "G"
- 10 S W Britton and V A Pertzoff (*by invitation*), *University of Virginia*  
Comparative effects of positive and negative accelerations
- 11 J R Poppen, Capt, M C, U S N, and D T Watts (*introduced by* D W Bronk), *Naval Air Experimental Station, Philadelphia*  
Human tolerance to high positive acceleration of short duration
- 12 O L Slaughter (*by invitation*) and E H Lambert, *Mayo Foundation*  
Plethysmographic study of leg volume changes in man during positive acceleration on a centrifuge
- 13 E H Lambert and O L Slaughter (*by invitation*), *Mayo Foundation*  
Venous pressure in the extremities of man during positive acceleration on a centrifuge
- 14 E H Wood, *Mayo Clinic and Foundation*  
Use of the valsalva maneuver to increase man's tolerance to positive acceleration
- 15 Philip Bard, C N Woolsey, R S Snider (*by invitation*), V B Mountcastle (*by invitation*) and R B Bromley (*by invitation*), *Johns Hopkins University School of Medicine*  
Delimitation of central nervous mechanisms involved in motion sickness
- 2 William Sangster (*by invitation*), M I Grossman and A C Ivy, *Northwestern University Medical School and University of Illinois College of Medicine*  
Influence of rate of gastric emptying upon the time onset of hunger contractions
- 3 W J Snape (*introduced by* J E Thomas), *Jefferson Medical College*  
The response of the gall bladder to various stimuli before and after vagotomy
- 4 M Eisenstein (*by invitation*) and H Necheles, *Michael Rees Hospital, Chicago*  
The sphincter of Oddi
- 5 Philip B Armstrong, *Syracuse University College of Medicine*  
Function in the developing liver
- 6 Martin Gutmann (*by invitation*), J Wenger (*by invitation*), and A C Ivy, *Northwestern University Medical School*  
The effect of sodium dehydrocholate on dog bile
- 7 Robert V Brown, *University of Tennessee Medical School and University of North Dakota*  
The effects of pilocarpine hydrochloride on hepatic bile secretion
- 8 B A Campbell (*by invitation*), Alan C Burton, P Fitzjames (*by invitation*), and A Bernstein (*by invitation*), *University of Western Ontario*  
Stratification of bile in the gall bladder and its relation to cholelithiasis
- 9 M H F Friedman and William J Snape (*by invitation*), *Jefferson Medical College*  
Pancreatic secretion in man in response to administration of secretin and insulin
- 10 I J Pincus (*by invitation*) and J E Thomas, *Jefferson Medical College*  
Correlation of pancreatic secretion and the pH of the duodenal content
- 11 J E Thomas and J O Crider, *Jefferson Medical College*  
Carbohydrates as stimuli for the secretion of pancreatic enzymes
- 12 Robert S Pogrund (*by invitation*), and F R Steggerda, *University of Illinois*  
A study of the behavior of various gases when placed in the colon of man
- 13 F R Steggerda and W C Clark (*by invitation*), *University of Illinois*  
The effects of the introduction of gas into the colon on its pressure and activity
- 14 J Clifford Stickney, David W Northup and Edward J Van Liere, *West Virginia University*  
Systemic blood pressure as a factor in the absorption of saline from the small intestine
- 15 Harry Greengard, M L Wolfrom (*by invitation*) and R K Ness (*by invitation*), *North*

## PHYSIOLOGY D

Wednesday 9 00 a m

ROOM 12, STEVENS HOTEL

### Gastro-intestinal Function

- 1 K Hwang (*by invitation*), M I Grossman and A C Ivy, *University of Illinois College of Medicine*  
The nervous control of the esophagus

- Systemic blood pressure as a factor in the absorption of saline from the small intestine
- 15 Harry Greengard, M L Wolfrom (*by invitation*) and R K Ness (*by invitation*), *North*

*western University Medical School and the Ohio State University*

The composition of crystalline secretin picrolonate

- 16 John W Sloan and John Van Prohaska (*introduced by G E Wakerlin*) *University of Illinois College of Medicine*

The use of jejunal transplants in the construction of ante-thoracic esophagus

### PHYSIOLOGY E

Wednesday 9 00 a m

ROOM 14, PALMER HOUSE

Joint Meeting with Society for Experimental Pathology

Coagulation

(For program see Pathology p 58)

### PHYSIOLOGY A

Wednesday, 2 00 p m

PRIVATE DINING ROOM 2, STEVENS HOTEL

#### General Physiology

- 1 J H Bodine and Laurence Fitzgerald (*by invitation*), *State University of Iowa*  
Riboflavin and other fluorescent compounds in a developing egg
- 1 H W Chalkley and George E Daniel (*by invitation*), *National Cancer Institute*  
"Secondary photosensitization" of hydra fusca after exposure to methyleholanthrene
- 3 Albert Bachem, *University of Illinois*  
Ultraviolet action spectra
- V F Lindeman (*introduced by Robert Gaunt*), *Syracuse University*  
The formation of acetylcholine in the developing retina of the chick embryo
- 5 C L Prosser, E E Painter and M N Swift (*by invitation*), *Argonne National Laboratory, Chicago, University of Illinois, and Loyola University School of Medicine*  
The clinical sequence of radiation damage
- 6 E E Painter, C L Prosser and M N Swift (*by invitation*), *Argonne National Laboratory, Chicago, Loyola University School of Medicine and University of Illinois*  
Nonspecificity of the patho-physiology of the radiation syndrome
- 7 S Rodbard, *Michael Reese Hospital*  
Body temperature arterial pressure relationship as a basis for physiological interpretation of diurnal rhythm
- 8 Paul Reaser and George Burch (*introduced by H S Mayerson*), *Tulane Medical School*  
Studies on sodium metabolism with a long half life radioactive sodium isotope

### BUSINESS MEETING

Wednesday 4 30 p m

NORTH BALLROOM, STEVENS HOTEL

### PHYSIOLOGY B

Wednesday 2 00 p m

NORTH BALLROOM, STEVENS HOTEL

#### Shock

- 1 Daniel L Kline (*introduced by Magnus I Gergersen*), *College of Physicians and Surgeons Columbia University*  
The effect of hemorrhage on the plasma amino nitrogen of the diabetic dog
- 2 Ewald E Selkurt, Robert S Alexander, and Mary B Patterson (*by invitation*), *Western Reserve Medical School*  
The role of the mesenteric circulation in the irreversibility of hemorrhagic shock
- 3 Robert S Alexander, *Western Reserve University School of Medicine*  
An analysis of the contour of the femoral arterial pulse in hemorrhagic shock
- 4 H Goldberg (*by invitation*), Frank Roemhild (*by invitation*), Harold C Wiggers and Raymond C Ingraham, *University of Illinois*  
The effect of pentobarbital anesthesia on the production of irreversible hemorrhagic shock
- 5 Raymond C Ingraham, Frank Roemhild (*by invitation*), Harold Goldberg (*by invitation*), and Harold C Wiggers, *University of Illinois*  
The treatment of impending hemorrhagic shock by means of pentobarbital sedation
- 6 Frank Roemhild (*by invitation*), Harold Goldberg (*by invitation*), Raymond C Ingraham and Harold C Wiggers, *University of Illinois*  
The effect of dibenamine on the production of irreversible hemorrhagic shock
- 7 Harold C Wiggers, Frank Roemhild (*by invitation*), Harold Goldberg (*by invitation*), and Raymond C Ingraham, *University of Illinois*  
The influence of prolonged vasoconstriction on the transition from impending to irreversible hemorrhagic shock
- 8 Harold D Green, J Maxwell Little, Joseph Hester (*by invitation*), and Helen Hilderman (*by invitation*), *Bowman Gray School of Medicine of Wake Forest College*  
Vasodilator substance present in urine
- 9 J Richard R Bobb (*introduced by Harold D Green*), *Bowman Gray School of Medicine*  
Role of the kidney in resistance to the ischemic compression shock
- 10 D D Munro (*by invitation*), and R L Noble, *McGill University, Montreal*

Changes in blood lymphocytes in normal and resistant rats following traumatic shock

- 11 M Katharine Cary (*by invitation*), Frank L Apperly (*by invitation*), and F A Hellebrandt, *Medical College of Virginia*

The influence of various physical therapeutic measures on the course of gravity shock

- 12 Edgar L Lipton (*by invitation*), Adam B Denison (*by invitation*), and Harold D Green, *Bowman Gray School of Medicine*

Influence of body temperature and of temperature of traumatized tissues upon local edema and survival of dogs subjected to ischemic compression trauma of their hind extremities

### BUSINESS MEETING

Wednesday 4 30 p m

NORTH BALLROOM, STEVENS HOTEL

### PHYSIOLOGY C

Wednesday 2 00 p m

PARLORS ABC, CONGRESS HOTEL

#### Muscle

- 1 Bernard F Wendt (*by invitation*) and A R McIntyre, *University of Nebraska College of Medicine*

The effect of d-Tubocurarine on spontaneous activity of frogs' sartorius muscle aroused by calcium lack

- 2 Alexander Sandow, *Washington Square College of Arts and Sciences, New York University*  
Latent period changes in non-propagated responses of normal and novocaine muscles

- 3 Bernard J Alpers, Richard G Berry, and Francis M Forster (*introduced by M H F Friedman*), *Jefferson Medical College*

The peripheral effect of curare on skeletal muscle fasciculations

- 4 Sheppard M Walker, *Washington University*  
The effect of desoxycorticosterone acetate and a low K diet on the action potentials induced in rat muscle by indirect stimulation

- 5 Kenneth C Fisher, James Hall (*by invitation*), and Joseph Stern (*by invitation*), *University of Toronto*

Insulin, citrate and the rate of oxygen consumption by isolated intact frog muscle

- 6 F A Fuhrman and J M Crismon, *Stanford University School of Medicine*

Changes in the distribution of sodium, potassium and water in muscle following release of tourniquets

- 7 Norma M Hajek (*by invitation*) and H M Hines, *State University of Iowa*

Experimental treatment of muscular spasticity

- 8 R Diaz-Guerrero and J D Thomson (*introduced by H M Hines*), *State University of Iowa*

Endocrine influences on muscle strength and neuromuscular atrophy and regeneration

### BUSINESS MEETING

Wednesday, 4 30 p m

NORTH BALLROOM, STEVENS HOTEL

### PHYSIOLOGY D

Wednesday, 2 00 p m

WEST BALLROOM, STEVENS HOTEL

#### Adrenal Cortex

- 1 Philip K Bondy and Frank L Engel (*introduced by Eugene A Stead, Jr*), *Emory University School of Medicine*

Urea synthesis in the adrenalectomized-nephrectomized rat on low potassium diet

- 2 Frank L Engel, E Irene Pentz, and Mildred G Engel (*introduced by Eugene A Stead, Jr*), *with the technical assistance of M Standifer Emory University*

The adrenal cortex and urea synthesis in the nephrectomized rat

- 3 Evelyn Howard, *Johns Hopkins University School of Medicine*

The effect of dietary factors on the adrenal X zone

- 4 Carmen B Casas (*by invitation*), Joseph T King and M B Visscher, *University of Minnesota Medical School*

Effect of caloric restriction on the development and function of adrenal cortical tumors in mice

- 5 Joseph T King, M B Visscher and Carmen B Casas (*by invitation*), *University of Minnesota Medical School*

Effect of gonadotropin on the function of adrenal cortical tumors in ovariectomized, restricted C<sub>3</sub>H mice

- 6 Lena A Lewis and Irvine H Page, *Cleveland Clinic Foundation*

Modifications in plasma protein pattern (Tiselius electrophoresis technique) in adrenalectomized and adrenalectomized hypertensive dogs

- 7 E M Landis and M Abrams (*by invitation*), *Harvard Medical School*

Choices of salts and water by normal and hypertensive rats with and without desoxycorticosterone

- 8 Dorothy Nelson (*introduced by J S Gray*), *Northwestern University Medical School*

Do rats select more sodium chloride than they need?

- 9 R G Grenell and E L McCawley (*by invitation*), *Yale University School of Medicine*  
The effects of adrenal cortical extract on the electroencephalogram

### BUSINESS MEETING

Wednesday, 4 30 p m

NORTH BALLROOM, STEVENS HOTEL

### PHYSIOLOGY E

Wednesday, 2 00 p m

PINE ROOM, CONGRESS HOTEL

#### Respiration

- 1 Franklin F Snyder, *Harvard Medical School*  
The oxygen concentration in the blood of breathing fetuses
- 2 Kenneth E Penrod and A H Hegnauer, *Boston University School of Medicine*  
The effect of pentothal sodium on blood gas transport
- 3 William B Draper, Richard W Whitehead and Joseph N Spencer (*by invitation*), *University of Colorado School of Medicine*  
Studies on diffusion respiration III Changes in alveolar gases and pH of venous blood
- 4 D H Barron, *Yale University School of Medicine*  
Oxygen dissociation curves of fetal and maternal sheep blood
- 5 J Percy Baumberger, *Stanford University*  
The reduction of oxygen by hemoglobin compounds in acid and a method of polarographic analysis
- 6 Wilson C Grant (*by invitation*) and Walter S Root, *College of Physicians and Surgeons, Columbia University*  
The relation of O<sub>2</sub> tension in bone marrow blood to the erythropoiesis following hemorrhage
- 7 H H Rostorfer and R H Rigdon (*by invitation*), *University of Arkansas School of Medicine*  
Isolation of erythroblasts from the blood of malarial infected ducks
- 8 W S Fowler (*by invitation*) and J H Comroe, Jr, *University of Pennsylvania*  
The rate of increase of arterial oxygen saturation following inspiration of 100% oxygen

### BUSINESS MEETING

Wednesday, 4 30 p m

NORTH BALLROOM, STEVENS HOTEL

### PHYSIOLOGY A

Thursday, 9 00 a m

NORTH ASSEMBLY ROOM, STEVENS HOTEL

#### General Physiology—Nerve

- 1 M G Larrabee, J M Posternak (*by invitation*), and D W Bronk, *University of Pennsylvania*  
Effects of chemical agents on metabolism and function of synapses and fibers in sympathetic ganglia
- 2 J M Posternak (*by invitation*), M G Larrabee, and D W Bronk, *University of Pennsylvania*  
Oxygen requirements of the neurones in sympathetic ganglia
- 3 D W Bronk, F Brink, C M Connelly (*by invitation*), F D Carlson (*by invitation*), and P W Davies (*by invitation*), *University of Pennsylvania*  
The time course of recovery oxygen consumption in nerve
- 4 L D Carlson, A W Martin, and K K Krauel (*by invitation*), *University of Washington*  
Studies concerning the role of metabolism in steady EMF maintenance under the influence of DNP
- 5 Abraham M Shanes, *Bermuda Biological Station, Marine Biological Laboratory, and New York University College of Dentistry*  
The effect of potassium on the injury potential of crab nerve
- 6 John H Welsh, *Harvard University*  
Repetitive discharge in crustacean axons
- 7 Harold T Gordon (*introduced by John H Welsh*), *Harvard University*  
Axon surface structure and interactions
- 8 Frank Brink, *University of Pennsylvania*  
Relation of optimum frequency for A C excitation to impulse frequency in chemically excited axons
- 9 E L Porter and P S Wharton (*by invitation*), *University of Texas*  
Increase in irritability of mammalian nerve in situ following ischemia
- 10 George W Stavraky and Charles G Drake (*by invitation*), *University of Western Ontario Medical School*  
An extension of the "Law of Denervation" to afferent neurones
- 11 J S Denslow (*introduced by Irvin M Korr*), *Still Memorial Research Trust, Kirksville, Mo*  
Double discharges in human motor units
- 12 David P C Lloyd, *Rockefeller Institute for Medical Research*  
Pattern of monosynaptic reflex connection between certain muscles of the ankle and digits

- 13 A K McIntyre (*by invitation*) and David P C Lloyd, *The Rockefeller Institute for Medical Research*  
Origin and distribution of some long spinal reflex effects on erural muscles

### PHYSIOLOGY B

Thursday, 9 00 a m

GRAND BALLROOM, STEVENS HOTEL

#### Heart

- 1 James E Eckenhoff, Joseph H Haskenschiel, Charles M Landmesser and Merel H Harmel (*introduced by Carl F Schmidt*), *University of Pennsylvania*  
The oxygen metabolism of the dog's heart
- 2 A Sidney Harris and Wilson P Matlock (*by invitation*), *Western Reserve University Medical School*  
The effects of anovemic anoxia upon conduction and excitability of mammalian cardiac muscle in situ
- 3 Thomas M Durant (*by invitation*), Joan Long (*by invitation*), and M J Oppenheimer, *Temple University School of Medicine*  
The effect of intravenous carbon dioxide on the initial ventricular deflection of the electrocardiogram
- 4 Emil Bozler, *Ohio State University*  
The time relations of the electric response of cardiac muscle
- 5 A S Gilson, Jr, *Washington University School of Medicine*  
Junctional delay in the heart of the turtle
- 6 J A E Eyster and W E Gilson (*by invitation*), *University of Wisconsin*  
Electrical characteristics of cardiac muscle injuries
- 7 H K Hellerstein (*by invitation*), and L N Katz, *Michael Reese Hospital*  
The effect of myocardial injury location on the S T segment displacement
- 8 Jane Sands Robb and William G Turman (*by invitation*), *Syracuse University*  
Variations in QT and in QT to cycle ratio
- 9 William G Turman (*by invitation*), Irving L Ershler (*by invitation*), and Jane S Robb, *Syracuse University*  
QT changes following exercise
- 10 R Langendorf (*introduced by L N Katz*), *Michael Reese Hospital*  
Concealed auriculo ventricular conduction, effect of blocked impulses on formation and conduction of subsequent impulses
- 11 Ronald Grant, M M Gertler and K Godwin Terroux (*introduced by H E Hoff*), *McGill University*

Adrenaline induced auricular fibrillation in the dog

- 12 Menard M Gertler and Dorothy Karp (*introduced by H E Hoff*), *McGill University*  
The effect of atabrine on the dog heart
- 13 H Stansfield (*by invitation*) and H E Hoff, *McGill University*  
Tetraethyl ammonium—potassium antagonism in the mammalian heart
- 14 W Edward Chamberlain (*by invitation*), Bert R Boone (*by invitation*), George F Ellinger (*by invitation*), George C Henny (*by invitation*) and Morton J Oppenheimer, *Temple University School of Medicine and U S Public Health Service*  
Asynchronism of ejection of the ventricles as measured with the electrokymogram

### PHYSIOLOGY C

Thursday, 9 00 a m

NORTH BALLROOM, STEVENS HOTEL

#### Biophysics—Temperature Regulation

- 1 A D Keller, *Baylor University College of Medicine*  
Descending nerve fibers subserving heat maintenance functions coursing with the cerebrospinal tracts through the pons
- 2 William W Chambers (*by invitation*) and William F Windle, *University of Washington Medical School*  
Site of action of a bacterial pyrogen in cats with central nervous system lesions
- 3 H C Bazett, L Love (*by invitation*), E S Mendelson (*by invitation*), and L H Peterson (*by invitation*), *University of Pennsylvania*  
Arterial temperatures in man
- 4 Hans O Haterius and George L Maison, *Boston University Medical School*  
Observations on hypothermia and rewarming in the dog Recovery from drastic reduction in body temperature
- 5 Allan Hemingway, *University of Minnesota Medical School*  
Recovery of temperature regulatory responses after ether anesthesia
- 6 James D Hardy, Ephraim Shorr, and Eugene F Du Bois, *Cornell University Medical College*  
Hormonal influence on basal metabolism of women in cold and warm environments
- 7 Fred C Heagy (*by invitation*) and Alan C Burton, *University of Western Ontario*  
The effect of magnesium on body temperature in the dog

- 8 Nathaniel Kleitman and Theodore Engelmann (by invitation), *University of Chicago*  
Diurnal cycle in activity and body temperature of rabbits
- 9 Douglas H K Lee and R F Riek (introduced by E F Adolph), *University of Queensland, Brisbane, Australia*  
Reactions of dairy cattle over a range of controlled temperatures and humidities
- 10 Walter C Randall, *St Louis University School of Medicine*  
Reflex sweating responses and the influence of arterial occlusion upon sweat gland activity
- 11 Edward D Palmes and Charles R Park (introduced by Ray G Daggs), *Armored Medical Research Laboratory*  
A technic of human calorimetry
- 12 J F Herrick, F H Krusen (by invitation), U M Leden (by invitation), and K G Wakim, *Mayo Foundation and Mayo Clinic*  
Experimental studies on microwaves and possible applications in physical medicine
- 13 M Tolpin (by invitation) and S Rodbard, *Michael Reese Hospital and University of Chicago*  
The body temperature-arterial pressure relationship in the chicken
- 14 C R Kemp (by invitation), W D Paul (by invitation), and H M Hines, *State University of Iowa*  
Studies on blood flow and the efficacy of deep tissue thermogenic agents
- 4 Lt John H Ivy (by invitation), Lt Forrest E Snapp (by invitation), and Capt Harry F. Adler, *School of Aviation Medicine*  
The relation between intracranial pressure and positive pressure breathing
- 5 A B Otis, D F Proctor (by invitation), and H Rahn, *University of Rochester School of Medicine and Dentistry*  
The measurement of alveolar pressure and the work of breathing
- 6 Lt Forrest E Snapp (by invitation), Lt John H Ivy (by invitation), and Capt Harry F Adler, *School of Aviation Medicine*  
The effect of various stimulant drugs on dogs made apneic by anoxia
- 7 James O Elam (by invitation), A Hemingway, and M B Visscher, *University of Minnesota*  
The distinction between alveolar and ventilatory types of pulmonary dysfunction
- 8 R W Stacy and W V Whitehorn (introduced by Fred A Hitchcock), *Ohio State University*  
The comparative susceptibility of cats and dogs to anoxia
- 9 H Rahn, A B Otis, and Wallace O Fenn, *University of Rochester School of Medicine and Dentistry*  
Alveolar gas changes during breath holding
- 10 George P Bain, Jack Q Sloan, and Marshall Brucer (introduced by Eric Ogden), *University of Texas and Scott and White Clinic*  
Depth of penetration of nebulized substances in the respiratory tree
- 11 David E Goldman (introduced by B G King), *National Naval Medical Center*  
The dependence of carbon monoxide uptake of the body on respiratory minute volume
- 12 W A Robbie (introduced by H M Hines), *State University of Iowa*  
The respiratory response of the rat to hydrogen cyanide poisoning
- 13 I Mack (by invitation), M Grossman (by invitation), and L N Katz, *Michael Reese Hospital*  
The effect of pulmonary congestion on distensibility of the lung

### PHYSIOLOGY D

Thursday, 9 00 a m

ROOM 12, STEVENS HOTEL

#### Respiration

- Clarence A Maaske, Donn L Smith (by invitation), and Robert F Rusk (by invitation), *University of Colorado School of Medicine*  
Respiratory responses resulting from varying degrees of temporary pulmonary artery occlusion in the anesthetized dog
- 2 Donn L Smith (by invitation), Robert F Rusk (by invitation), and Clarence A Maaske, *University of Colorado School of Medicine*  
Respiratory responses resulting from temporary pulmonary artery occlusion in the intact unanesthetized dog
- 3 Florence W Haynes, Thomas D Kinney (by invitation), Harper K Hellems (by invitation), and Lewis Dexter (by invitation), *Peter Bent Brigham Hospital and Harvard Medical School*  
Circulatory changes in experimental pulmonary embolism

### PHYSIOLOGY E

Thursday, 9 00 a m

ROOM 18, PALMER HOUSE

#### Carbohydrate Metabolism

- 1 Nathan Lifson, Victor Lorber, Warwick Sakami (by invitation), and Harland G Wood (by invitation), *University of Minnesota Medical School and Western Reserve University Medical School*

Pathways of conversion of butyrate carbon to rat liver glycogen

- 2 L A Crandall, Jr, Alys Lipsecomb (by invitation), and S B Barker, *University of Tennessee*

Sources for hepatic glucose production in fasting normal and diabetic dogs

- 3 D J Ingle, M C Prestrud (by invitation), and M H Kuizenga (by invitation), *The Upjohn Company*

Effect of adrenal cortex extract on glucose tolerance in eviscerated rats

- 4 Theodore Gillman, Joseph Gillman, and Joel Mandelstam (introduced by C I Reed), *University of the Witwatersrand, Johannesburg, So Africa*

Studies of carbohydrate metabolism in South African negro pellagrins I Oral and intravenous glucose tolerance tests

- 5 James A Greene, *Baylor University College of Medicine*

Alteration of carbohydrate metabolism in hypopituitarism in man

- 6 John R Brown (by invitation), Andrew A Ormsby (by invitation), Byron M Hendrix, (by invitation), and D Bailey Calvin, *University of Texas*

The relative effectiveness of fructose and glucose in the alleviation of insulin shock

- 7 J A Dye and Barbara A Woodward (by invitation), *Cornell University*

Alloxan diabetes in the sheep

- 8, R Tislow and Anette Chesler (by invitation), *Biological Research Laboratories, Schering Corporation*

Effect of bal in preventing alloxan diabetes in rats

- 9 R G Janes and J M Brady (introduced by W R Ingram), *State University of Iowa College of Medicine*

Thiamine deficiency in adult normal and diabetic rats as studied under paired-feeding conditions

- 10 R Levine and B Huddleston (by invitation), *Michael Reese Hospital*

The comparative action of insulin on the disposal of intravenous fructose and glucose

- 11 F C Dohan and F D W Lukens, *University of Pennsylvania*

Experimental diabetes mellitus produced by intraperitoneal injections of glucose

- 12 Roger M Reinecke, Guilford G Rudolph, and Melvin Bryson (introduced by Leo T Samuels), *University of Utah*

The effect of ureteral ligation, mercury bichloride and phloridzin on the glucogenic function of the kidney of the eviscerated rat (Pharm)

## PHYSIOLOGY A

Thursday, 2 00 p m

NORTH BALLROOM, STEVENS HOTEL

### General Physiology—Membranes and Colloids

- 1 J F Manery, K C Fisher, and E Moore (by invitation), *University of Toronto, Canada*  
Water intake and membrane hardening of fish eggs
- 2 A A Warren (by invitation), K C Fisher, and J F Manery, *University of Toronto, Toronto, Canada*  
Calcium ions and the development of hardness in the eggs of speckled trout
- 3 Walter S Wilde, Roy O Scholz (by invitation), and Dean B Cowie (by invitation), *Carnegie Institution of Washington and Johns Hopkins University*  
Turnover rate of sodium in the aqueous humor of the eye measured by radiosodium Na<sup>24</sup>
- 4 Oscar Hechter, *Worcester Foundation for Experimental Biology*  
The nature of the barrier to the diffusion of intradermally injected fluids
- 5 M H Jacobs and Marian Willis (by invitation), *University of Pennsylvania*  
Observations on the antihemolytic action of sucrose
- 6 Eugene D Robin (by invitation), Abraham Dury (by invitation), Leonard Essman (by invitation), and Chester E Leese, *George Washington University Medical School*  
The effect of urethane upon the erythrocyte membrane
- 7 Richard R Overman, *University of Tennessee College of Medicine*  
Reversible permeability alterations in the erythrocytes of the malarious monkey
- 8 Cecil K Drinker and Esther Hardenbergh (by invitation), *Harvard School of Public Health*  
Absorption from the pulmonary alveoli
- 9 John H Grindlay, James C Cain (by invitation), Jesse L Bollman (by invitation), Eunice Flock (by invitation), and Frank C Mann, *The Mayo Foundation*  
Experimental study of lymph collected continuously from liver and thoracic duct
- 10 Robert Chambers and Alfred L Copley, *New York University*  
A method and observations on capillary glitis in rabbits
- 11 R G Mrazek, Jr (by invitation) Reed, *University of Illinois*  
The effect of fatigue on
- 12 David F Waugh *W Technology*



- A comparison of the regeneration products of fibrous insulin with native insulin
- 13 B J Luyet and P M Gehleno (*by invitation*), *St Louis University and Biodynamica Laboratory*  
Thermoelectric recording of ice formation and of vitrification during ultra rapid cooling of protoplasm

### PHYSIOLOGY B

Thursday, 2 00 p m

LOWER TOWER ROOM, STEVENS HOTEL

#### Enzymology

- 1 J N Stannard and B L Horecker (*by invitation*), *National Institute of Health*  
The *in vitro* inhibition of cytochrome oxidase by azide and cyanide
- 2 B L Horecker (*by invitation*) and J N Stannard, *National Institute of Health*  
The cytochrome c-azide complex
- 3 John M Reiner (*by invitation*) and S Spiegelman, *Washington University School of Medicine*  
Comparison of the mechanisms whereby  $\text{N}_2\text{N}_5$  and 2,4 dinitrophenol suppress anaerobic carbohydrate assimilation
- 4 S Spiegelman, John M Reiner (*by invitation*), and M Sussman (*by invitation*), *Washington University School of Medicine*  
Adaptation to a substrate in the absence of its utilization
- 5 Dorothy J McLean (*by invitation*) and Kenneth C Fisher, *University of Toronto*  
The oxygen consumption during the assimilation of nitrogen sources by the bacterium *Serratia marcescens*
- 6 I H Broh-Kahn (*by invitation*) and I Arthur Mirsky, *May Institute for Medical Research of the Jewish Hospital Cincinnati*  
The inhibition of inorganic phosphate liberation in the presence of hexokinase activity
- 7 Ernst Fischer, Ernst Huf (*by invitation*), V W Ramsey (*by invitation*), and C R Ryland (*by invitation*) *Medical College of Virginia*  
Adenosinetriphosphatase activity of myosin from denervated skeletal muscle
- 8 A R McIntyre and Irvin Braverman (*by invitation*), *University of Nebraska College of Medicine, Omaha*  
The actions of certain drugs on intact myosin-ATP system
- 9 Clifford A Angerer and Jorge Gonzalez Q (*by invitation*), *The Ohio State University*  
The effect of various substrates on the oxygen consumption of heart muscle of the adrenalectomized rat

- 10 Jorge Gonzalez Q (*by invitation*) and Clifford A Angerer, *The Ohio State University*  
The effect of adrenalectomy on the oxygen consumption of testis of testosterone-treated normal rats
- 11 I Arthur Mirsky and R H Broh-Kahn (*by invitation*), *May Institute for Medical Research of the Jewish Hospital, Cincinnati*  
The catheptic activity of tissues of normal and alloxanized rats
- 12 Alfred F Bliss (*introduced by David Rapport*), *Tufts College Medical School*  
Enzyme formation of retinal vitamin A

### PHYSIOLOGY C

Thursday 2 00 p m

UPPER TOWER ROOM, STEVENS HOTEL

#### Central Nervous System

- 1 B Libet and J B Kahn, Jr (*by invitation*), *University of Chicago*  
Steady potentials and neurone activity in mammals
- 2 Harry D Patton (*introduced by Curt P Richter*), *The Johns Hopkins Hospital*  
Sympathetic innervation of the cat's footpad
- 3 Thomas J Holbrook (*by invitation*) and C G de Gutierrez-Mahoney, *St Vincent's Hospital, N Y*  
Diffusion of painful stimuli over segmental, infrasegmental and suprasegmental levels of the spinal cord
- 4 Leonard W Jarcho (*introduced by Philip Bard*), *Johns Hopkins University School of Medicine*  
Excitability of cortical afferent systems in relation to anesthesia
- 5 Stuart Abel and Stanley C Harris (*introduced by John S Gray*), *Northwestern University Medical School*  
Morphine Benzadrine analgesia in obstetrics
- 6 Stanley C Harris and Frances J Friend (*introduced by J S Gray*), *Northwestern University Dental School and Medical School*  
Contribution of adrenals to morphine analgesia
- 7 Broda O Barnes, *Kingman, Ariz*  
Headache—etiology and treatment
- 8 A A Schiller and H L Jones (*introduced by C I Reed*), *U S Naval Hospital and Naval Medical Research Institute*  
Subjective responses to small reductions in biometric pressure in subjects with functional joint pathology
- 9 Robert F Heimbürger (*introduced by L W Freeman*), *The Chicago Memorial Hospital*  
Physiological factors in neurogenic bladders

- 10 L W Freeman and R F Heimbürger (by invitation), *Kennedy Veterans' Administration Hospital, Memphis*  
Spasticity in transverse lesions of the spinal cord in humans
- 11 G M Everett (introduced by R K Richards), *Abbott Laboratories*  
The effect of d-tubocurarine on the central nervous system
- 12 W Raab (introduced by F J M Sichel), *University of Vermont*  
An epinephrine-like catechol compound in the brain

### PHYSIOLOGY D

Thursday, 2 00 p m

PINE ROOM, CONGRESS HOTEL

#### Pituitary and Thyroid

- 1 Kendrick Hare, *Cornell University Medical College*  
The nervous control of the release of pituitrin
- 2 Stanley L Wallace (by invitation), Edwards C Whatley (by invitation), George A Anderson (by invitation), and J Maxwell Little, *The Bowman Gray School of Medicine*  
The effect of pitressin on the excretion of chloride and water in the human
- 3 Carroll A Handley (by invitation) and A D Keller, *Baylor University College of Medicine*  
Morphine induced secretion of pitressin in dogs with hypophyseal stalk section
- 4 Raymond Gregory and Glenn A Drager (by invitation), *University of Texas Medical Branch*  
The effect of pancreatectomy on the hypophysis
- 5 Hubert R Catchpole, *University of Illinois College of Medicine*  
Cellular distribution of glycoprotein in the anterior lobe of the pituitary gland
- 6 R E Haist and E J Pugh (by invitation), *University of Toronto, Canada*  
A method of estimating the total volume of the pancreatic islets in small animals
- 7 S B Barker, *State University of Iowa*  
Effect of dimethylphenols on rat thyroids
- 8 K E Paschke, A Cantarow, and W Peacock (by invitation), *Jefferson Medical College and Massachusetts Institute of Technology*  
Influence of female sex hormone on uptake of radioactive iodine by the thyroid
- 9 James H Leatham and Robert D Seeley (by invitation), *Rutgers University*  
The influence of hypothyroidism on plasma and liver protein concentrations

### PHYSIOLOGY

#### Papers Read by Title

- 1 Shannon C Allen, *Wright Field*  
Ability of human subjects to withstand "explosive compression"
- 2 William F Allen, *University of Oregon Medical School*  
Bark used for the response in a positive conditioned reflex
- 3 Alice M Bahrs and Rosalind Wulzen, *Oregon State College*  
Effect of deficiency in anti stiffness factor on relative arterial occlusion pressure of guinea pigs
- 4 T C Barnes, *Hahnemann Medical College and Hospital of Philadelphia*  
Outline of a method of procedure in electroencephalography
- 5 T C Barnes, *Hahnemann Medical College and Hospital of Philadelphia*  
Transient phase boundary potentials which resemble the nerve impulse
- 6 T C Barnes, *Hahnemann Medical College and Hospital of Philadelphia*  
Electrical action of anticonvulsant drugs
- 7 T C Barnes, *Hahnemann Medical College and Hospital of Philadelphia*  
Mechanism of Action of Prostrigmine
- 8 T C Barnes and Marie D Amoroso (by invitation), *Hahnemann Medical College and Hospital of Philadelphia*  
Electroencephalograms correlated with scores of the bell adjustment inventory for personality
- 9 T C Barnes and Marie D Amoroso (by invitation), *Hahnemann Medical College and Hospital of Philadelphia*  
Bioelectrical studies of fatigue III Further studies of alleged mental fatigue in students
- 10 T C Barnes and Marie D Amoroso (by invitation), *Hahnemann Medical College and Hospital of Philadelphia*  
Use of pentothal in electroencephalography of babies
- 11 T C Barnes and R Beutner, *Hahnemann Medical College and Hospital of Philadelphia*  
On the role of acetylcholine and esterase during nerve activity
- 12 Clarissa H Beatty (introduced by Magnus I Gregersen), *College of Physicians and Surgeons, Columbia University*  
The arterial blood glucose level in alloxan diabetic dogs subjected to hemorrhage
- 13 J R R Bobb (by invitation) and Harold D Green, *Bowman Gray School of Medicine*  
Absence of any influence of heparin upon ischemic compression shock studied at various environmental temperatures

- 14 Stanley E Bradley, John J Curry, and Geraldine P Bradley (*introduced by Hans O Haterius*), *Boston University School of Medicine and the Evans Memorial, Massachusetts Memorial Hospitals*  
Renal extraction of P-aminohippurate in normal subjects and in essential hypertension and chronic diffuse glomerulonephritis
- 14 Stanley E Bradley and Meyer H Halperin (*introduced by Hans O Haterius*), *Boston University School of Medicine and the Evans Memorial, Massachusetts Memorial Hospital*  
Renal oxygen consumption and sodium P-aminohippurate (PAH) extraction in normal man during abdominal compression
- 15 C G Breckenridge (*introduced by A D Keller*), *Baylor University College of Medicine*  
Retention of sex functions after isolation of pars anterior by extirpation of the hypophysial stalk
- 16 C G Breckenridge (*introduced by A D Keller*), *Baylor University College of Medicine*  
Intracellular granules in the hypothalamus and infundibulum of the dog
- 17 C G Breckenridge (*by invitation*) and A D Keller, *Baylor University College of Medicine*  
Immediate and permanent dwarfing with subsequent sexual development following near-ordinary hypophysectomy in three-months old female puppy
- 18 Reg B Bromley (*introduced by Philip Baird*), *Johns Hopkins University*  
Conditioned responses in a decorticate dog
- 19 H D Bruner, *University of Pennsylvania*  
The hot wire anemometer as a flowmeter
- 20 L D Carlson and H L Burns (*by invitation*), *University of Washington*  
A method suitable for application of moist heat therapy and applicable for controlling moist chambers
- 21 L D Carlson, W R Lovelace, II (*by invitation*), and H L Burns (*by invitation*), *University of Washington*  
Oxygen requirements in commercial aviation as determined by physiologic, medical and engineering bases
- 22 Samuel A Corson and Otto C Elmer (*by invitation*), *University of Minnesota School of Medicine*  
Measurement of total and bicarbonate base of urine by the cation resin exchange and electro dialysis methods
- 23 J M Crismon and F A Fuhrman, *Stanford University*  
Production of regional ischemia by intravascular injection of glass and plastic microspheres in graded sizes
- 24 B Dauber (*by invitation*), L Horlick (*by invitation*), and L N Katz, *Michael Reese Hospital*  
The protective action of thyroid and potassium iodide in cholesterol induced atherosclerosis in chickens
- 25 John E Davis and Wilburn M Hamilton (*by invitation*), *University of Arkansas School of Medicine*  
The influence of folic acid on serum cholinesterase activity in human subjects
- 26 G G Deanin (*by invitation*) and F R Steggerda, *University of Illinois*  
The use of the spectrophotometer for measuring changes in skin reflectance in *Rana pipiens*
- 27 Richard C de Bodo and Kathryn F Prescott (*by invitation*), *New York University College of Medicine*  
The relationship of insulin hypersensitivity to increased sugar utilization
- 28 C F Dick (*by invitation*), J F Bosma (*by invitation*), and E Gellhorn, *University of Minnesota*  
Contracture and suppression of cortical activity
- 29 Victor A Drill and Aldo P Truant (*by invitation*), *Yale University School of Medicine*  
Influence of thyroid gland on the conversion of carotene to vitamin A
- 30 A L Dunn (*by invitation*) and A R McIntire, *University of Nebraska College of Medicine*  
Rectangular pulse generator for stimulating tissue
- 31 Abraham Dury (*by invitation*), Eugene D Robin (*by invitation*), and Chester E Leese, *George Washington University Medical School*  
The effect of different grades of penicillin on the motility of the rabbit uterus
- 32 John Field, II and Ruth L Dryer (*by invitation*), *Stanford University*  
Effect of sodium caprylate on the thermal stability of the respiratory system in rat brain
- 33 M H F Friedman, B F Haskell (*by invitation*), and William J Snape (*by invitation*), *Jefferson Medical College*  
Treatment of non-specific ulcerations of the intestinal tract with extracts of intestinal mucosa
- 34 M H F Friedman and Elizabeth N King (*by invitation*), *Jefferson Medical College*  
Presence of a specific gastric hormone (gastrin) in the dog's pyloric mucosa

- 35 Robert Gaunt and Mildred Liling (*by invitation*), *New York and Syracuse Universities*  
The effects on rats of large doses of an estrogen, the methyl ether of bis dehydrodoisynolic acid
- 36 Ernst Gellhorn, *University of Minnesota Medical School*  
Patterns of muscular innervation in man
- 37 Theodore Gillman, Joseph Gillman, and Joel Mandelstam (*introduced by C I Reed*), *University of Witwatersrand, Johannesburg, So Africa*  
Studies of carbohydrate metabolism in South African negro pellagrins II Insulin-adrenal tolerance tests
- 38 Jorge Gonzalez Q (*by invitation*) and Clifford A Angerer, *Ohio State University*  
The effect of various substrates on the oxygen uptake of thymus in adrenalectomized rats
- 39 Jorge Gonzalez Q (*by invitation*) and Clifford A Angerer, *Ohio State University*  
Weight changes in various endocrine glands of normal rats after prolonged treatment with testosterone
- 40 R G Grenell and H S Burr (*by invitation*), *Yale University School of Medicine*  
Surface potentials and peripheral nerve regeneration
- 41 M H Halperin, C K Friedland, and R W Wilkins (*introduced by H O Haterius*), *Boston University School of Medicine and Evans Memorial, Massachusetts Memorial Hospitals*  
The effect of local compression upon blood flow in the extremities of man
- 42 W F Hamilton and John W Remington, *University of Georgia School of Medicine*  
Modifications in the method for calculating stroke volume from the central pressure pulse contour
- 43 James D Hardy and Helen Goodell (*by invitation*), *Cornell University Medical College*  
Thermoregulatory phenomena associated with exposure to warm and cold environment
- 44 James D Hardy, Harold C Wolff, and Helen Goodell (*by invitation*), *Cornell University Medical College*  
Intensity discrimination of pain sensation
- 45 A Sidney Harris and Wilson P Matlock (*by invitation*), *Western Reserve University School of Medicine*  
Effects of anovenic anoxia upon refractoriness of mammalian cardiac muscles in situ
- 46 Eleanor Clarke Hay, *Institut de Medecine et de Chirurgie experimentales, Université de Montreal*  
Hepato and nephrotoxic effect of glycine
- 47 R C Herrin and C C Lardinois (*by invitation*), *University of Wisconsin*  
Renal clearance of citrate in dogs
- 48 E Homburger (*by invitation*), B Etsten (*by invitation*), and H E Himwich, *Albany Medical College and Medical Division, Edgewood Arsenal*  
Factors influencing the susceptibility of rats to barbiturates
- 49 C Riley Houck, Richard J Bing, Frank N Craig, and Frank E Visscher (*introduced by Homer W Smith*), *New York University College of Medicine*  
Renal hyperemia in the dog after intravenous infusion of adenosine, adenylic acid, or adenosinetriphosphate
- 50 C Riley Houck (*by invitation*), Betty Crawford (*by invitation*), James H Bannon (*by invitation*), and Homer W Smith, *New York University College of Medicine*  
Mechanism of death in dogs following the intravenous injection of nitrogen mustards
- 51 Herbert P Jacoby (*by invitation*), James W Chappell (*by invitation*), and Sergius Morgulis, *University of Nebraska College of Medicine*  
Some effects of alpha tocopheryl phosphate on enzymatic activity
- 52 Irwin H Kaiser (*introduced by S R M Reynolds*), *Carnegie Institution of Washington*  
Effects of atropine and estrogens on endometrial blood vessels in intraocular transplants
- 53 Irwin H Kaiser (*introduced by S R M Reynolds*), *Carnegie Institution of Washington*  
Modification by anti-histaminic agents of estrogenic effects on endometrial blood vessels in intraocular transplants
- 54 A D Keller, *Baylor University College of Medicine*  
Failure of sexual development following lesions in environs of the pinna in "senior" female pups
- 55 A D Keller and C G Breckenridge (*by invitation*), *Baylor University College of Medicine*  
Retention of normal insulin tolerance and adrenal cortex following extirpation of hypophysial stalk in dog
- 56 R F Kline, *University of Virginia*  
Effects of severe anoxia and their amelioration
- 57 S A Komarov, Richard Kolm and Harry Shay, *Temple University School of Medicine*  
Excretion of neutral red by the liver and kidneys

- 58 S W Kuffler, Y Laporte, and R E Ransmeier (*introduced by* R W Gerard), *University of Chicago*  
Reflex activity of the frog's small-nerve motor system
- 59 Eleanor M Larsen (*introduced by* Walter J Meek), *University of Wisconsin*  
The effect of the fatigue of static effort upon stance oscillations
- 60 Eleanor M Larsen (*introduced by* Walter J Meek), *University of Wisconsin*  
The effect of the fatigue of static effort and of continued standing upon the point of balance in recumbency
- 61 Richard E Lee and Nina Zworykin Lee (*introduced by* Magnus I Gregersen), *College of Physicians and Surgeons, Columbia University*  
The peripheral vascular system and its reactions in scurvy. An experimental study
- 62 R Levine and B Huddleston (*by invitation*), *Michael Reese Hospital*  
The mode of excretion of fructose by the dog
- 63 W D Lotspeich (*by invitation*) and R F Pitts, *Syracuse University College of Medicine*  
The role of amino acids in the renal tubular secretion of ammonia
- 64 Esther L McCandless (*by invitation*) and J A Dye, *Cornell University*  
Effects of alloxan administration in the calf
- 65 J F McClendon and William C Foster (*by invitation*), *Hahnemann Medical College*  
The thyroid gland of the smallest mammal
- 66 Paul L McLain and C H William Ruhe (*introduced by* C C Guthrie), *University of Pittsburgh*  
Observations on the dilution principle of relative serum volume estimation
- 67 David I Macht and Marcus Ostro (*by invitation*), *Sinai Hospital*  
Phytotoxic reactions of normal and irradiated blood sera
- 68 David I Macht and Marcus Ostro (*by invitation*), *Sinai Hospital*  
Influence of X-rays on the thromboplastic and phytotoxic properties of penicillin and streptomycin
- 69 David I Macht, *Sinai Hospital*  
Influence of antibiotics and sulfonamides on the growth of yeast
- 70 David I Macht, *Sinai Hospital*  
Thromboplastic properties of penicillin and streptomycin
- 71 David I Macht, *Sinai Hospital*  
Influence of penicillin and streptomycin on the behavior of rats
- 72 S H Macht (*by invitation*), M H F Friedman, and B H Malone (*by invitation*), *Jefferson Medical College*  
The relation of stomach shape to emptying time
- 73 George L Maison and Hans O Haterius, *Boston University Medical School*  
Terminal changes in cardiac activity and in respiration in death from severe hypothermia
- 74 N S R Maluf, *Harvard Medical School*  
The effect of interpleural adhesions on pulmonary expansion and venous pressure
- 75 N S R Maluf, *Harvard Medical School*  
A method for the measurement of velocity and volume-flow of blood in the inferior vena cava of intact dogs
- 76 M Marks (*by invitation*), M Spiegel-Adolf (*by invitation*), and E A Spiegel, *Temple University*  
Effect of cerebral concussion upon chemically induced convulsions
- 77 S O Mast, *Johns Hopkins University*  
The process of feeding in paramecium
- 78 S O Mast, *Johns Hopkins University*  
Changes in the food-vacuole and digestion in paramecium
- 79 Walter J Meek, J A E Eyster, J W Stutzman, and W E Gilson (*by invitation*), *University of Wisconsin*  
Electrical phenomena in mammalian smooth muscle
- 80 A T Milhorat and O Diethelm (*by invitation*), *Cornell University Medical College*  
Substances in blood of patients during emotional states. Effect on the isolated rabbit intestine
- 81 Campbell Moses (*introduced by* C C Guthrie), *University of Pittsburgh*  
Diurnal variation in the specific gravity of the blood, serum, corpuscles and hematocrit reading
- 82 David W Northup, J Clifford Stickney, and Edward J Van Liere, *West Virginia University School of Medicine*  
Effect of hemorrhage on intestinal absorption of chloride in the presence of sulphate
- 83 M Jane Oesterling (*by invitation*) and William T Salter, *Yale University School of Medicine*  
Micro-colorimetric determination of urinary estrogens over short periods of time
- 84 A G Oliver (*by invitation*) and A D Keller, *Baylor University College of Medicine*  
The immediate effects of varying degrees of hypophysectomy in the previously pancreatized dog
- 85 O Sidney Orth, Milton Davis (*by invitation*), and Jane M Moir (*by invitation*), *University of Wisconsin Medical School and State of Wisconsin General Hospital*  
Clinical experience with use of the pneumatic balance resuscitator

- 86 David T Overbey (by invitation), Antonio Ramirez (by invitation), C J Wiggers, and Hampden C Lawson, *University of Louisville*  
Bleeding volume and blood volume in hemorrhagic shock
- 87 Richard R Overman, Theron S Hill (by invitation), and Hudson Jost (by invitation), *University of Tennessee College of Medicine*  
Ionic balance and correlated psycho-physiological measurements in premenstrual tensional states
- 88 Richard R Overman, A K Davis (by invitation), and Elva Tharp (by invitation), *University of Tennessee College of Medicine*  
Blood and "extracellular" fluid volumes and ionic balance in human therapeutic malaria
- 89 Edward D Palmes and Charles R Park (introduced by Ray G Daggs), *Armored Medical Research Laboratory*  
Thermocouples for the measurement of the surface temperature of the skin
- 90 Edward D Palmes (introduced by Ray G Daggs), *Armored Medical Research Laboratory*  
An apparatus and method for the continuous measurement of evaporative water loss from human subjects
- 91 Kenneth E Penrod, *Boston University School of Medicine*  
Chronic toxicity of hexachlorocyclohexane and its gamma-isomer (Gammaxene) in rats
- 92 Naomi E Pettengill (by invitation) and Arthur W Martin, *University of Washington*  
The amounts of connective tissue in various muscles of the dog with some interspecific comparisons
- 93 Charles S Petty (by invitation) and Arthur W Martin, *University of Washington*  
Some observations on the effect of thouracil and dimtrophenol on the chick metabolic rate
- 94 B P Reed (by invitation) and C I Reed, *University of Illinois*  
X-ray diffraction studies on human dental enamel
- 95 C I Reed, *University of Illinois*  
Hypocalcemia and hypervitaminosis D
- 96 C I Reed and B P Reed (by invitation), *University of Illinois*  
Electron microscopy of erythrocytes from dog blood
- 97 C I Reed, *University of Illinois*  
A modification of manual method of artificial respiration
- 98 C I Reed and B P Reed (by invitation), *University of Illinois*  
Electron microscopy of bull sperm
- 99 Warren S Rehm and Lowell E Hokin (by invitation), *University of Louisville School of Medicine*  
Effect of hydrochloric acid on the potential of the resting and secreting stomach
- 100 Warren S Rehm and Lowell E Hokin (by invitation), *University of Louisville School of Medicine*  
The effect of applied current on the potential between a dead stomach and HCL
- 101 S R M Reynolds and I H Kaiser (by invitation), *Carnegie Institution of Washington*  
Application of the strain gage dynamometer to quantitative evaluation of uterine activity in experimental animals
- 102 S R M Reynolds, *Carnegie Institution of Washington*  
Differential uterine tensions and the flow of maternal blood through the uterus during pregnancy
- 103 Monroe J Romansky, Eugene D Robin, and Lois Gnagy (introduced by C E Leese), *Walter Reed General Hospital*  
A study of urinary gonadotropin output in patients with testicular tumor
- 104 Jane Sands Robb and Cornelius T Kaylor (by invitation), *Syracuse University*  
The conducting system in human foetal hearts and implications regarding Q T based thercon
- 105 N P Scala (by invitation) and E A Spiegel, *Temple University*  
Depression of labyrinthine excitability by acoustic stimuli
- 106 S Rodbard (with the technical assistance of L Taylor) *Michael Reese Hospital*  
Evidence for a temperature sensitive center in a poikilotherm, the turtle
- 107 I H Rozenfeld (by invitation), R W Gerard, L H Boyarsky (by invitation), and J B Smyth (by invitation), *University of Chicago*  
An instrument to measure muscle tonus in man
- 108 A H Ryan and L B Nice, *Chicago Medical School*  
Effect of morphine and certain other drugs on a sympathetic reaction in man
- 109 Walter B Shelley and Frank M Melton (by invitation), *University of Pennsylvania*  
Studies on absorption through normal human skin
- 110 Landrum B Shettles, *Johns Hopkins Hospital*  
Effects of low oxygen tension on fertility in adult male guinea pigs

- 111 F J Sichel and Cheryl Parkhurst (by invitation), *University of Vermont College of Medicine*  
The role of potassium in conduction of the impulse in striated muscle
- 112 Ernst Simonson and Ancel Keys, *University of Minnesota*  
Energy cost in horizontal and grade walking of poliomyelitis patients
- 113 Irwin W Sizer, *Massachusetts Institute of Technology*  
The oxidation of certain amino acids and proteins by peroxidase and hydrogen peroxide
- 114 Jay A Smith (introduced by L B Nice), *Chicago Medical School*  
Lack of effect of a digitalis preparation on the blood pressure decrease caused by aminophyllin
- 115 Wilbur K Smith, *University of Rochester*  
The differential action of erythroidine in the normal and in the decerebrate animal
- 116 A Sokalchuk (introduced by E A Spiegel), *Temple University Medical School*  
Blood pressure in seasickness
- 7 E A Spiegel, A J Lee (by invitation), M Marks (by invitation), and M Spiegel-Adolf (by invitation), *Temple University*  
Changes of the electrical discharges of the hypothalamus and midbrain tegumentum in cerebral concussion
- 18 E A Spiegel and A Sokalchuk (by invitation), *Temple University*  
Influence of medication upon blood pressure in seasickness
- 119 J W Stutzman, Quill Murphy (by invitation), and C R Allen, *University of Wisconsin and University of Texas*  
Further studies on the production of cyclopropane epinephrine tachycardia
- 120 J E Thomas, *Jefferson Medical College*  
The intestinal pH threshold for regulation of gastric emptying
- 121 Julian M Tobias and Rosemary Holmes (by invitation), *University of Chicago*  
Observations on the use of the oxygen cathode
- 122 Julian M Tobias, *University of Chicago Toxicity Laboratory*  
Studies on the sodium, potassium and water content of tissues in the cockroach (*periplaneta americana*)
- 123 Robert D Tschirgi (introduced by R W Gerard), *University of Chicago*  
Further analysis of the gasp reflex
- 124 Caroline Tum-Suden, *Boston University School of Medicine*  
The effect of ergotamine tartrate on potassium tolerance
- 125 David B Tyler, *California Institute of Technology*  
The effect of benzedrine and certain barbiturates during prolonged wakefulness
- 126 David B Tyler, J Goodman (by invitation), and T Rothman (by invitation), *California Institute of Technology*  
The effect of mental "activity" and experimental insomnia on the electrical activity of the brain
- 127 Edward J Van Liere, J Clifford Stickney, and David W Northup, *West Virginia University*  
Effect of stimulation of carotid sinus region on absorption from small intestine
- 128 G van Wagenen, *Yale University School of Medicine*  
Maturity induced by testosterone in the young male monkey
- 129 G E Wakerlin, H Minatoya (by invitation), T Lefco (by invitation), John Marshall (by invitation), and Rufus Walker (by invitation), *University of Illinois College of Medicine*  
Further observations on the prophylaxis of experimental renal hypertension with renal extracts
- 130 K G Wakim, U M Leden (by invitation), F H Krusen (by invitation), and J F Herrick, *Mayo Foundation and Mayo Clinic*  
The effects of heating by microwaves on venous return
- 131 John R Whittier (by invitation) and Fred A Mettler, *Columbia University College of Physicians and Surgeons*  
Subthalamic lesion in the primate
- 132 G C Wickwire and Ruth Krouse (introduced by W E Burge), *University of Illinois*  
The effects of carbon dioxide on insulin convulsions and brain potential
- 133 Rosaline L Wilhelm (by invitation), Warren E Gilson (by invitation), and O Sidney Orth, *State of Wisconsin General Hospital and University of Wisconsin Medical School*  
Pressures produced in the respiratory tract of anesthetized patients during spontaneous, controlled or artificial respiration
- 134 J H Wills, *University of Tennessee*  
Studies on the mechanism of action of veratrine upon the neuromuscular system
- 135 C N Woolsey, H-T Chang (by invitation), and P Bard, *Johns Hopkins University*  
Distribution of cortical potentials evoked by electrical stimulation of dorsal roots in *macaca mulatta*
- 136 H T Wyss (by invitation), M Marks (by invitation), and E A Spiegel, *Temple University*  
Effect of cerebral concussion upon the threshold of electrically induced convulsions

- 137 B W Zweifach, Ephraim Shorr, and S Baez  
(by invitation), *Cornell University Medical  
College and the New York Hospital*

Hepato renal factors in circulatory homeos-  
tasis, XI A vaso excitor principle in the  
blood of hypertensive dogs

## THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

### THIRTY-EIGHTH ANNUAL MEETING

#### BIOCHEMISTRY A

Monday, 9 00 a m

NORTH ASSEMBLY ROOM, STEVENS HOTEL

##### Inhibitors of Enzyme Action

- 1 Hans Lineweaver and C W Murray (by  
invitation), *Western Regional Research Labo-  
ratory, Albany, California*  
Apparent identity of antitrypsin of egg white  
and ovomucoid
- 2 Donald E Bowman, *Indiana University  
School of Medicine, Indianapolis*  
Further differentiation of bean antitryptic  
factors
- 3 Eugene C Loomis (introduced by Olver  
Kamm), *Parke, Davis and Company, Detroit*  
Fibrinolysin and antifibrinolysin
- 4 Albert Dorfman, Melvin L Ott, and Elizabeth  
J Reimers (introduced by Ralph I Dorfman),  
*Army Medical Center, Washington, D C*  
The determination of antihyaluronidase in  
human blood
- 5 J Raymond Klein and Norman S Olsen  
(by invitation), *University of Illinois College  
of Medicine, Chicago*  
Inhibition of d-amino acid oxidase by kojic  
acid
- 6 John O Hutchens and Thomas McMahon  
(introduced by Franklin C McLean), *Uni-  
versity of Chicago*  
Effect of sodium fluoroacetate on oxidative  
steps of carbohydrate metabolism
- 7 D W Wilson, Adelaide M Elluva (by invita-  
tion), and Samuel Gurin, *University of  
Pennsylvania, Philadelphia*  
The metabolic fate of radioactive lactate in the  
phlorhizimized animal
- 8 Thomas P Singer (introduced by H G Wood),  
*Western Reserve University School of Medi-  
cine, Cleveland*  
On the mechanism of enzyme inhibition by  
sulphydryl reagents
- 9 E S Guzman Barron, and Sherman Dickman  
(by invitation), and T P Singer (by invita-  
tion), *University of Chicago*

The inhibition of enzymes by ionizing radia-  
tions

- 10 K A C Elliott and Marion K Birmingham  
(by invitation), *McGill University, Montreal,  
Can*

The effects of pH on the respiration of brain  
slices

#### BIOCHEMISTRY B

Monday, 9 00 a m

PRIVATE DINING ROOM 2, STEVENS HOTEL

##### Lipids

- 1 DeWitt Stetten, Jr and William H Goldwater  
(by invitation), *Columbia University, New  
York*  
The origin of certain fetal metabolites
- 2 W R Bloor, *University of Rochester, Rochester,  
N Y*  
A colorimetric method for the determination  
of small amounts of lipid
- 3 Aaron Bodansky, *Hospital for Joint Diseases,  
New York*  
The significance of border line values of serum  
free cholesterol
- 4 W C Hess, *Georgetown Medical School, Wash-  
ington, D C*  
Chromatographic separation of cholesterol and  
cholesterol esters from blood plasma
- 5 Alfred E Koehler and Elsie Hill (by invita-  
tion), *Santa Barbara Cottage Hospital and  
the Sansum Clinic Research Foundation,  
Santa Barbara, Calif*  
Molecular sublimation and distillation of  
cholesterol and its esters
- 6 E V Flock, J C Cain (by invitation), J H  
Grindlay, and J L Bollman, *The Mayo  
Foundation, Rochester, Minn*  
Phospholipids of lymph following feeding of  
fat to dogs
- 7 R G Sinclair, *Queen's University, Kingston,  
Canada*  
The composition of serum phospholipids
- 8 L B Macpherson (by invitation) and Colin C  
Lucas, *University of Toronto, Toronto, Can*  
Inositol containing phospholipid of rat liver



- 9 Jordi Folch, *McLean Hospital, Waverley, and Harvard Medical School, Boston*  
Isolation of a soybean phosphatide containing carbohydrate, inositol and glycerol as constituents
- 10 Paul L Munson (*by invitation*), Mary Ellen Jones (*by invitation*), Arthur E Heath (*by invitation*), and F C Koch, *Armour Laboratories, Chicago*  
Isolation of alpha-mono-palmitin from pancreas
- 11 William A Horwitz (*by invitation*) and Warren M Sperry, *New York State Psychiatric Institute and Hospital*  
Biochemical changes in the blood following electric shock therapy

## BIOCHEMISTRY C

Monday, 9 00 a m

WEST BALLROOM, STEVENS HOTEL

## Proteins

- 1 Max A Lauffer, *University of Pittsburgh*  
Crystallization of tobacco mosaic virus by serum albumin
- 2 Frank W Putnam (*introduced by W R Tweedy*), *Camp Detrick, Frederick, Md*  
Physical chemical properties of crystalline botulinus A toxin
- 3 C A Knight, *Rockefeller Institute for Medical Research, Princeton, N J*  
Biochemical studies on highly purified preparations of influenza A and B viruses
- 4 Dempsey Morrison and Harold A Jeskey (*by invitation*), *University of Tennessee, Memphis*  
The pigment, lipids and proteins of the malaria parasite (*P knowlesi*)
- 5 Abraham Mazur and Ephraim Shorr, *Cornell University Medical College and the New York Hospital, New York*  
Hepato renal factors in circulatory homeostasis, IX properties of a partially purified hepatic vaso-depressor principle
- 6 R F Furchgott (*by invitation*) and Ephraim Shorr, *Cornell University Medical College and the New York Hospital, New York*  
Hepato-renal factors in circulatory homeostasis, X an hepatic enzyme system which inactivates an hepatic vaso-depressor (Physiol)
- 7 F Lee Rodkey (*by invitation*) and Eric G Ball, *Harvard Medical School, Boston*  
Oxidation-reduction potentials of cytochrome C
- 8 Christopher Carruthers (*introduced by H A Mattill*), *Barnard Free Skin and Cancer*

*Hospital and the Department of Anatomy, Washington University School of Medicine, St Louis*

- Polarographic determination of cytochrome C
- 9 M Laskowski, Anna Kazenko (*by invitation*), and Cecilia K Keith (*by invitation*), *Marquette Medical School, Milwaukee*  
Attempts to identify a new crystalline protein from beef pancreas as a proteolytic zymogen
- 10 Walter H Seegers, Robert C Murphy (*by invitation*), Arnold G Ware (*by invitation*), Stephen R Bodnar (*by invitation*), and M Mason Guest, *Wayne University College of Medicine, Detroit*  
A substance derived from bovine plasma which produces leucopenia and lowers blood pressure
- 11 John Fuller Taylor, *Washington University School of Medicine, St Louis*  
The purification of phosphofructokinase from rabbit muscle

## BIOCHEMISTRY D

Monday, 9 00 a m

ENGLISH WALNUT ROOM, CONGRESS HOTEL

## Micro-Organisms

(Nutrition and Metabolism)

- 1 Ralph W McKee, Quentin M Geiman (*by invitation*), and Theodore S Cobbe, Jr (*by invitation*), *Harvard Medical School, Boston*  
Amino acids in the nutrition and metabolism of malarial parasites
- 2 Rollin D Hotchkiss, *Rockefeller Institute for Medical Research, New York*  
The assimilation of amino acids by respiring washed staphylococci
- 3 M John Boyd (*by invitation*), Milan A Logan, and Alfred A Tytell (*by invitation*), *University of Cincinnati College of Medicine*  
Growth Requirements of *Clostridium welchii*
- 4 John R Totter and Edith S Sims (*by invitation*), *University of Arkansas, Little Rock*  
Studies on the function of pteroylglutamic acid in *Streptococcus faecalis*
- 5 George H Hitchings and Elvira A Falco (*by invitation*), *The Wellcome Research Laboratories, Tuckahoe, N Y*  
The occurrence and isolation of the pneumonia-susceptibility factor
- 6 Willis A Gortner and Frances E Volz (*introduced by L A Maynard*), *Cornell University, Ithaca, N Y*  
The maintenance of *L casei* and *L arabinosus* cultures in the lyophilized state

- 7 L M Henderson (*by invitation*) and Esmond E Snell, *University of Wisconsin, Madison*  
A uniform medium for microbiological determination of amino acids with various test organisms
- 8 Gerrit Toennies and Dorothy Leaf Gallant (*by invitation*), *Lankenau Hospital Research Institute and Institute for Cancer Research, Philadelphia*  
A study of experimental variables in the bacteriological determination of amino acids (Microbiological Assay)
- 9 H E Carter, R K Clark, Jr (*by invitation*), Edwin H Flynn (*by invitation*), Betty Lytle (*by invitation*), and Mary Robbins (*by invitation*), *Noyes Laboratory of Chemistry, Urbana*  
Oxidation of meso-inositol by acetobacter suboxydans

## JOINT SESSION OF THE FEDERATION

1 45 p m

GRAND BALLROOM, STEVENS HOTEL

Program on p 3

## BIOCHEMISTRY BUSINESS MEETING

Monday, 4 15 p m

GRAND BALLROOM, STEVENS HOTEL

## BIOCHEMISTRY A

Tuesday, 9 00 a m

NORTH BALLROOM, STEVENS HOTEL

## Carbohydrate Metabolism

- 1 Otto Meyerhof and Peter Oesper (*by invitation*), *University of Pennsylvania, Philadelphia*  
The oxidative reaction of fermentation
- 2 Alan H Mehler (*by invitation*), Arthur Kornberg (*by invitation*), Sanitago Grisolia (*by invitation*), and Severo Ochoa, *New York University College of Medicine*  
The specificities of some dehydrogenases toward pyridine nucleotides
- 3 Gerty T Cori and Milton W Stein (*by invitation*), *Washington University School of Medicine, St Louis*  
Glucose- and fructosekinase in mammalian tissues
- 4 M F Utter, *Western Reserve University, Cleveland*  
Inactivation of phosphohexokinase in brain
- 5 E Racker and I Krinsky (*introduced by Alwin M Pappenheimer, Jr*), *New York University*  
Inhibition of glycolysis in mouse brain homogenates by ferrous sulfate (Immunol)

- 6 A B Hastings, C B Anfinsen, R G Gould (*by invitation*), I N Rosenberg (*by invitation*), and A K Solomon (*by invitation*), *Harvard Medical School, Boston*  
In vitro observations on  $C^{14}O_2$  incorporation in liver glycogen
- 7 Victor Lorber (*by invitation*), Nathan Lifson (*by invitation*), Warwick Sakami (*by invitation*), and Harland G Wood, *Minnesota College of Medicine, Minneapolis, and Western Reserve University School of Medicine, Cleveland*  
Conversion of propionate carbon to liver glycogen in the intact rat, studied with  $c^{13}$ -labeled propionate
- 8 Norman S Olsen (*by invitation*) and J Raymond Klein, *University of Illinois, Chicago*  
Hyperglycemia following intravenous injection of insulin preparations
- 9 Earl W Sutherland (*by invitation*) and Carl F Cori, *Washington University School of Medicine, St Louis*  
Influence of insulin on glycogen synthesis and breakdown in liver slices

## BIOCHEMISTRY B

Tuesday, 9 00 a m

PRIVATE DINING ROOM-2, STEVENS HOTEL

## Steroids

- 1 William H Fishman (*introduced by E A Evans, Jr*), *University of Chicago*  
Beta-flucuronidase in the metabolic conjugation of estrogenic hormones
- 2 Robert W Bates and Herman Cohen (*by invitation*), *E R Squibb and Sons, New Brunswick, N J*  
Quantitative fluorescent micro method for the determination of natural estrogens
- 3 Erma v O Miller, Olaf Mickelsen, and Ancel Keys, *University of Minnesota, Minneapolis*  
The excretion of 17 ketosteroids by normal young men
- 4 W H Pearlman, K E Paschkis, A E Rakoff (*by invitation*), A Cantarow and A A Walkling (*by invitation*), *Jefferson Medical College, Philadelphia*  
The metabolism of estrone in the dog
- 5 Leo T Samuels and Mary Pottner (*by invitation*), *University of Utah Medical School, Salt Lake City*  
The metabolism of testosterone by the livers of different species of animals
- 6 Bernard B Longwell and F X Gassner (*by invitation*), *University of Colorado School of Medicine, Denver, and Colorado Agricultural Experiment Station, Fort Collins*

The fecal excretion of androgens by the pregnant cow

- 7 Charles Tesar (*by invitation*), Evelyn Borgstrom (*by invitation*), J R Xenos (*by invitation*), and R F Gallagher, *University of Chicago, Chicago*

Rearrangement of steroid ring C ketols in alkali

- 8 Seymour Lieberman (*by invitation*), Konrad Dobriner, and C P Rhoads (*by invitation*), *Memorial Hospital, New York*

The isolation of metabolites of adrenal cortical hormones from human urine

- 9 Ralph W McKee, Theodore S Cobbe, Jr (*by invitation*), and Quentin M German (*by invitation*), *Harvard Medical School, Boston*

Observations on the action of ascorbic acid in adrenal cortical function

### BIOCHEMISTRY C

*Tuesday, 9 00 a m*

WEST BALLROOM, STEVENS HOTEL

#### Proteins (continued)

- 1 G Robert Greenberg (*by invitation*) and Cyrus P Barnum, *Western Reserve University, Cleveland, and University of Minnesota, Minneapolis*

Effect of pH on apparent pK of phenolic groups in protein

- 2 Samuel Gurin and Adelaide M Delluva (*by invitation*), *University of Pennsylvania, Philadelphia*

The biological conversion of radioactive phenylalanine to adrenalin

- 3 John W Mehl, Richard J Winzler, and Eva Pacovaka (*by invitation*), *University of Southern California School of Medicine, Los Angeles*

The Biuret reaction The measurement of the amount of copper bound

- 4 Arnold J Rawson (*by invitation*) and F Wilham Sunderman, *University of Pennsylvania, Philadelphia*

The calcium binding property of the serum proteins

- 5 John G Reinhold and Harrison F Flippin (*by invitation*) with the technical assistance of Elaine Clausen (*by invitation*), *Philadelphia General Hospital, Philadelphia*

Basic and acid groups of serum proteins in disease

- 6 Dean Burk, John Hearon (*by invitation*), Hilton Levy (*by invitation*), and Arthur L Schade (*by invitation*), *National Institute of Health, Bethesda (Md), and Overly Biochemical Research Foundation, New York*

Reversible oxygenation of cobaltodihistidine to oxybis (cobaltodihistidine), and comparisons with other metal-amino acids, oxyhemoglobin, and oxyhemocyanin

- 7 Douglas A Macfadyen, *Presbyterian Hospital of the City of Chicago*

Spectroradiometry of ninhydrin and some of its derivatives

- 8 K A Kuikin (*by invitation*) and Carl M Lyman, A and M College of Texas, *College Station*

Factors which influence the stability of tryptophane during the hydrolysis of proteins in alkaline solution

### BIOCHEMISTRY D

*Tuesday, 9 00 a m*

NORTH ASSEMBLY ROOM, STEVENS HOTEL

#### Antimetabolites, Antibiotics

- 1 J R Haag, P H Weswig (*by invitation*) and Anna May Freed (*by invitation*), *Oregon State College, Corvallis*

Antithiamine activity of bracken fern (Immunol)

- 2 Gladys A Emerson, *Merck Institute for Therapeutic Research, Rahway, N J*

The antivitamin B<sub>6</sub> activity of desoxypyridoxine in the rat (Immunol)

- 3 Oliver H Gaebler and E V Herman (*by invitation*), *Henry Ford Hospital, Detroit*

Metabolism experiments with antimetabolites

- 4 Heinrich Waelsch and Ernest Borek (*by invitation*), *New York State Psychiatric Institute and Hospital and Columbia University, New York*

The antimetabolite effect of the optical isomers of the sulfoxide derived from methionine

- 5 Ernest Borek (*by invitation*) and Heinrich Waelsch, *New York State Psychiatric Institute and Hospital and Columbia University, New York*

Homologues of methionine sulfoxide as glutamic acid antimetabolites

- 6 Sidney W Fox, Marguerite Fling (*by invitation*), Yutaka Kobayashi (*by invitation*), and Frederick N Minard (*by invitation*), *Iowa State College, Ames*

Inhibition of bacterial growth by amino acid enantiomorphs and their derivatives

- 7 Ella H Fishberg, Erich Seligmann (*by invitation*), and Michael Wassermann (*by invitation*), *Beth Israel Hospital, New York*

Relation of reducing intensity to streptomycin susceptibility of bacteria

- 8 George E Boxer and Viola C Jehneek (*by invitation*), *Merck and Company, Inc, Rahway, N J*

A chemical method for the determination of streptomycin in blood

- 9 William H Elliott, (by invitation), Philip A Katzman, Sidney A Thayer, and Edward A Doisy, *Saint Louis University School of Medicine, St Louis*

Chemical studies on the antibiotic, fumigacin

- 10 R E Feenev (by invitation), E M Humphreys (by invitation), H D Lightbody and J A Garibaldi (by invitation), *Western Regional Research Laboratory, Albany, Calif*

Nutritional studies on the formation of subtilin by *Bacillus subtilis* in surface cultures

- 11 Alden K Boor, C Phillip Miller and Walter D Hawk (by invitation), *University of Chicago*

Protection of mice from the lethal action of some bacterial endotoxins by penicillin administered previously

## BIOCHEMISTRY

Tuesday, 2 00 p m

GRAND BALLROOM, STEVENS HOTEL

### Symposium on the Chemistry and Metabolism of Nucleic Acids and Their Constituents

H S Loring, *Chairman*

- 1 J P Greenstein, *National Cancer Institute, Bethesda, Md*

Enzymatic degradation of the nucleic acids

- 2 C A Zittle, *Biochemical Research Foundation, Newark, Del*

Hydrolysis of ribo- and deoxyribonucleic acids with phosphoesterase from calf intestinal mucosa

- 3 H K Mitchell and M B Houlahan, *Kerckhoff Laboratory of Biological Sciences, California Institute of Technology, Pasadena*

Investigations on the biosynthesis of pyrimidine nucleosides in *Neurospora*

- 4 H S Loring, G L Ordway, J G Pierce, and P M Roll, *Stanford University, Stanford University, Calif*

A microbiological method of assay for the pyrimidine ribonucleosides and ribonucleotides

- 5 J G Pierce and H S Loring, *Stanford University, Stanford University, Calif*

Purine and pyrimidine antagonism in the pyrimidine-deficient *Neurospora* No 1298

- 6 G B Brown, P M Roll, and A A Plentl, *The Sloan Kettering Institute for Cancer Research, New York*

Studies on the metabolism of adenine

## BIOCHEMISTRY A

Wednesday, 9 00 a m

UPPER TOWER ROOM, STEVENS HOTEL

### Metabolism of Amino and Keto-Acids

- 1 Arthur Kornberg (by invitation), Severo Ochoa, and Alan H Mehler (by invitation), *New York University College of Medicine*

Spectrophotometric studies on the decarboxylation of beta-ketoacids

- 2 Severo Ochoa, Alan H Mehler (by invitation), and Arthur Kornberg (by invitation), *New York University College of Medicine*

Reversible oxidative decarboxylation of malic acid

- 3 Dean Watt (by invitation) and Lester O Krampitz, *Western Reserve University, Cleveland*

Alpha-oxetolactic acid, and intermediate in acetyl methylcarbinol formation

- 4 Dana I Crandall (by invitation), Samuel Gurin, and D Wright Wilson, *University of Pennsylvania, Philadelphia*

Studies on the formation of isotopic acetate in homogenized liver

- 5 Nathan O Kaplan (by invitation) and Fritz Lipmann, *Massachusetts General Hospital, Boston*

The mechanism of enzymatic acetylation

- 6 Fritz Lipmann, Nathan O Kaplan (by invitation), and G David Novelli (by invitation), *Massachusetts General Hospital, Boston*

Chemistry and distribution of the coenzyme for acetylation (coenzyme A)

- 7 Philip P Cohen and R W McGilvery (by invitation), *University of Wisconsin, Madison*

Synthesis of *p* aminohippuric acid by liver homogenates

- 8 Philip P Cohen and Mika Hayano (by invitation), *University of Wisconsin, Madison*

Synthesis of urea by rat liver homogenates

- 9 John J Speck (introduced by E A Evans, Jr), *University of Chicago*

The enzyme synthesis of glutamine

- 10 Charles E Carter (by invitation) and Jesse P Greenstein, *National Institute of Health, Bethesda, Md*

The acceleration of enzymatic desamidation of glutamine by certain inorganic anions

## BIOCHEMISTRY B

Wednesday, 9 00 a m

PRIVATE DINING ROOM 2, STEVENS HOTEL

### Choline, Methionine, Transmethylation, etc

- 1 Camillo Artom and W E Cornatzer (by invitation)

tion), *Wale Forest College, Winston-Salem, N C*

Action of choline and fat on the formation of liver phospholipids

- 2 E A Sellers, (introduced by C H Best), *University of Toronto, Toronto, Canada*

The hypotrophic factors in the treatment of carbon tetrachloride cirrhosis in rats

- 3 Mary C Bucciero (by invitation) and James M Orten, *Wayne University College of Medicine, Detroit*

The effects of certain amino acids and choline on the production of polycythemia by cobalt (Immunol)

- 4 N H Horowitz, *California Institute of Technology, Pasadena*

The formation of methionine from cysteine in *Neurospora*

- 5 Henry Borsook and Jacob W Dubnoff, *California Institute of Technology, Pasadena*

Oxidative and non-oxidative transmethylation reaction

- 6 Robert E Olson (by invitation), Howard A Eder (by invitation), and Fredrick J Stare, *Harvard School of Public Health and Harvard Medical School, Boston*

Excretion of glycoeyamine by rats on low methionine, low choline diets

- 7 Eugene Roberts and Charles J Spiegl (introduced by Harold C Hodge), *University of Rochester, Rochester, N Y*

Influence of dietary protein, methionine and cysteine on vitamin C synthesis in the rat

### BIOCHEMISTRY C

Wednesday, 9 00 a m

WEST BALLROOM, STEVENS HOTEL

#### Amino Acids

- 1 Anthony A Albanese, L Emmett Holt, Jr, Virginia Irby (by invitation), Selma E Snyderman (by invitation), and Marilyn Lein (by invitation), *New York University College of Medicine*

The tryptophane requirement of the infant

- 2 L Emmett Holt, Jr, Anthony A Albanese, Virginia Irby (by invitation), Selma E Snyderman (by invitation), and Marilyn Lein (by invitation), *New York University College of Medicine*

The isoleucine requirement of the infant

- 3 Stanley W Hier (by invitation) and Olaf Bergeim, *University of Illinois College of Medicine, Chicago*

Influence of ingestion of single amino acids on the blood level of free amino acids

- 4 J D Solomon (by invitation), S W Hier (by

invitation), and Olaf Bergeim, *University of Illinois College of Medicine, Chicago*

Free amino acids in cerebrospinal fluid

- 5 Cecil C Harvey (by invitation) and M K Horwitt, *Elgin State Hospital, Elgin, Ill*

Amino acid excretion in the urine

- 6 H E Sauberlich (by invitation), E L Pearce (by invitation), and C A Baumann, *University of Wisconsin, Madison*

Amino acid excretion by mice fed deficient diets (Immunol)

- 7 B S Schweigert (by invitation) and P B Pearson, *A and M College of Texas, College Station*

Metabolism of tryptophane by vitamin B<sub>6</sub> deficient rats and mice

- 8 Julius White and Florence R Write (by invitation), *United States Public Health Service, Bethesda, Md*

Effect of cystine, lysine, and tryptophane on the growth of rats ingesting certain carcinogenic agents

### BIOCHEMISTRY D

Wednesday, 9 00 a m

LOWER TOWER ROOM, STEVENS HOTEL

#### Blood

- 1 Armand J Quick, *Marquette University School of Medicine, Milwaukee*

Quantitative studies on the coagulation defect in hemophilia

- 2 Mario Stefanni (by invitation) and Marcel C Blanchaer, *Marquette University School of Medicine, Milwaukee*

On the quantitative relationship between the concentration of calcium and the coagulation of the blood

- 3 Zacharias Dische and Karl Meyer, *Columbia University, New York*

Observations on the composition of heparin and the nature of its hexuronic constituents

- 4 Arnold G Ware (by invitation), M Mason Guest, and Walter H Seegers, *Wayne University, Detroit*

Stability of prothrombin

- 5 M E Muhrer (by invitation) and A G Hogan, *University of Missouri, Columbia*

Hemostatic properties of hemolytic agents

- 6 H B Collier, *University of Saskatchewan, Saskatoon*

Kinetics of hemolysis by lysolecithin

- 7 S S Spicer, C H Hanna, and Ariel M Clark (introduced by H D Baernstein), *National Institute of Health, Bethesda, Md*

In vitro methemoglobin reduction in intact erythrocytes

- 8 Helmut R Gutmann (*by invitation*), Bernard J Jandorf, and Oscar Bodansky, *Edgewood Arsenal, Maryland*

The role of methylene blue and pyridien nucleotides in the reduction of methemoglobin in hemolyzates

- 9 Edwin E Hays and Elizabeth C Paulsen (*by invitation*), *University of Vermont College of Medicine, Burlington*

An in-vitro method for studying various substances upon red cell maturation

## BIOCHEMISTRY

Wednesday, 2 00 p m

GRAND BALLROOM, STEVENS HOTEL

### Symposium on Fat Metabolism

William C Stadie, *Chairman*

- 1 Samuel Gurin, *University of Pennsylvania, Philadelphia*

The biological formation and oxidation of ketone bodies

- 2 Albert L Lehninger, *University of Chicago*

The fatty acid oxidase system

- 3 David Rittenberg, *Columbia University, New York*

Relation of acetic acid to lipid metabolism

- 4 David Green, *Columbia University, New York*

On the enzyme systems which oxidize fatty acids in animal tissues

- 5 Cohn C Lucas and Charles H Best, *University of Toronto, Toronto, Can*

Recent work on the lipotropic factors

## BUSINESS MEETING

Wednesday, 4 50 p m

GRAND BALLROOM, STEVENS HOTEL

## BIOCHEMISTRY A

Thursday, 9 00 a m

UPPER TOWER ROOM, STEVENS HOTEL

### Nucleic Acids and Related Compounds

- 1 Max M Friedman and Alfred Angrist (*introduced by Kurt G Stern*), *Polytechnic Institute, Brooklyn, and Queens General Hospital, Jamaica, New York*

Nucleotide and nucleic acid content of human tissues

- 2 Alex B Novikoff (*by invitation*) and Van R Potter, *University of Wisconsin, Madison*

Changes in nucleoprotein concentration in regenerating liver

- 3 Kurt G Stern, G Goldstein (*by invitation*),

J Wagman (*by invitation*), and J Schryver (*by invitation*), *Polytechnic Institute, Brooklyn*

Studies on desoxyribonucleoproteins Isolation and properties of genoprotein T

- 4 Donald Visser, Irving Goodman, and Karl Dittmer (*introduced by Robert C Lewis*), *University of Colorado, Boulder*

The synthesis and biological properties of some new thymine and uracil nucleosides

- 5 F Schlenk and M J Waldvogel (*by invitation*), *University of Texas, M D Anderson Hospital for Cancer Research, Houston*

The fate of ribose in nucleoside degradation

- 6 S Rapoport and Robert H Wagner (*by invitation*), *University of Cincinnati*

The occurrence of 2 phospho ribo-trihydroxyglutaric acid in liver

- 7 J M Wiame (*introduced by Carl F Cori*), *Washington University School of Medicine, St Louis*

Yeast metaphosphate

- 8 Gerhard Schmidt, Liselotte Hecht (*by invitation*), and S J Thannhauser, *Tufts Medical School, Boston*

Observations concerning the assimilation of inorganic phosphate by Bakers' yeast

- 9 P K Stumpf (*introduced by H B Lewis*), *University of Michigan, Ann Arbor*

Phosphorylated carbohydrate compounds in developing chick embryo

## BIOCHEMISTRY B

Thursday, 9 00 a m

PRIVATE DINING ROOM 2, STEVENS HOTEL

### Radio Isotopes, Bone Studies

- 1 Waldo E Cohn, *Clinton Laboratories, Oak Ridge, Tenn*

The preparation of fission radioisotopes for radiotoxicological studies

- 2 W D Armstrong, *University of Minnesota, Minneapolis*

Turnover of bone measured with radiophosphorus

- 3 Harold Carpenter Hodge, Marlene Falkenheim (*by invitation*), and Elizabeth Emery (*by invitation*), *University of Rochester School of Medicine and Dentistry, Rochester, N Y*

Calcium exchange in bone using radiocalcium in vitro

- 4 L Van Middlesworth, D H Copp, and J G Hamilton (*introduced by J M D Olmsted*), *University of California, Berkeley*

Uptake of plutonium, yttrium and strontium by the callus of healing bone fractures (Physiol)

- 5 D Harold Copp, Marian J Chace, and Florence Duffy (introduced by David M Greenberg), University of California Medical School, Berkeley

Effects of severe phosphorus deficiency on the metabolism and histology of bone

- 6 Philip Handler and John McCoy (by invitation), Duke University School of Medicine, Durham, N C

The significance of parathyroid activity in physiological regulation of acid-base balance

### BIOCHEMISTRY C

Thursday, 9 00 a m

WEST BALLROOM, STEVENS HOTEL

#### Nitrogen Metabolism, Liver Regeneration

- 1 Felix Friedberg (by invitation), Harold Tarver (by invitation), and David M Greenberg, University of California Medical School, Berkeley

Studies in endocrine regulation of protein synthesis with isotopic amino acids I Hyperinsulinism

- 2 Harry M Vars and Fraser N Gurd (by invitation), University of Pennsylvania, Philadelphia

The influence of dietary protein upon the regeneration of liver protein in the rat

- 3 Fraser N Gurd (by invitation), Harry M Vars, and I S Ravdin (by invitation), University of Pennsylvania, Philadelphia

The relation of nitrogen metabolism to the regeneration of liver protein

David L Drabkin, University of Pennsylvania, Philadelphia

Liver regeneration and cytochrome c metabolism

- 5 Leon Miller (introduced by W H Pearlman), The Jefferson Medical College, Philadelphia

Changes in rat liver enzyme activity with inanition

- 6 J B Allison, R D Seeley (by invitation), and F P Ferguson (by invitation), Rutgers University, New Brunswick, N J

The determination of nitrogen balance indexes of protein hydrolysates in dogs

- 7 C F Kade, Jr (by invitation), J Houston (by invitation), Wm A Phillips (by invitation), and M Sahyun, Sterling Drug, Inc, Detroit

Minimum protein and amino acid requirement for maintenance of nitrogen equilibrium in dogs

- 8 Robert H Silver, Irwin Clark, E E Howe, and Curt C Porter (introduced by Edgar G Miller), Merck Institute for Therapeutic Research

and the Merck Research Laboratories, Rahway, N J

The maintenance of dogs on a diet containing amino acids as the source of nitrogen

- 9 Warren M Cox, Jr, Arthur J Mueller (by invitation), Robert Elman (by invitation), Anthony A Albanese, and L Emmett Holt, Jr, Mead Johnson and Company, Washington University School of Medicine and Barnes Hospital, St Louis, and New York University and Bellevue Hospital, New York

Species difference in nitrogen retention, the effect of adding methionine to an enzymic casein hydrolysate

### BIOCHEMISTRY D

Thursday, 9 00 a m

LOWER TOWER ROOM, STEVENS HOTEL

#### Vitamins

- 1 Olaf Mickelsen and Ancel Keys, University of Minnesota, Minneapolis

The urinary vitamin excretion of young men during rehabilitation following semistarvation

- 2 Saul H Rubin (by invitation) and Elmer L Sevringhaus, Hoffmann-LaRoche, Inc, Nutley, N J

The urinary excretion of B-vitamins by surgical patients during intravenous feeding

- 3 R M Johnson (by invitation) and C A Baumann, University of Wisconsin, Madison

Studies on the role of the kidney in vitamin A metabolism

- 4 Albert E Sobel, Sidney P Gottfried (by invitation), and Benjamin Kramer, The Jewish Hospital of Brooklyn

Vitamin A serum levels in mongolism following vitamin A ingestion in oily and aqueous media

- 5 Ruth Okey, Samuel Lepkovsky, and Richard Peneharz (by invitation), University of California, Berkeley, and Mt Zion Hospital, San Francisco

The effect of biotin deficiency on liver cholesterol storage in rats

- 6 R H McCoy, A E Axelrod, and K Hofmann (introduced by H E Longenecker), University of Pittsburgh and Western Pennsylvania Hospital, Pittsburgh

Oxybiotin metabolism in the chick

- 7 Jean E Robinson (by invitation), Nora Levitas (by invitation), Fred Rosen (by invitation), and W A Perlzweig, Duke University School of Medicine, Durham, N C

Fluorometric method for determination of the pyridine nucleotides in animal tissues

- 8 Harold C Goldthorpe and Doris Tippit, Univer-

sity of Utah Medical School, Salt Lake City

The estimation of nicotinic acid in tissues

- 9 W O Caster (*by invitation*), Olaf Michelsen, and Ancel Keys, *University of Minnesota, Minneapolis*

A study of the yeast fermentation method for the determination of thiamine and pyrimin

## BIOCHEMISTRY A

Thursday, 2 00 p m

GRAND BALLROOM, STEVENS HOTEL

### Photosynthesis and Plant Enzymes

- 1 A H Brown (*by invitation*), E W Fager (*by invitation*), and H Gaffron, *University of Chicago*

Use of carbon 14 in the study of photosynthesis

- 2 Harland Wood and George O Burr, *Western Reserve University, Cleveland, Experiment Station HSPA, Honolulu*

Photosynthesis with  $C^{14}O_2$  and the distribution of heavy carbon in the sugars

- 3 C S French, R W Smith (*by invitation*), and F D H Macdonald (*by invitation*), *University of Minnesota, Minneapolis*

Dye reduction by chloroplast suspensions as a means of measuring their activity for photosynthetic oxygen evolution

- 4 Robert MacVicar (*by invitation*) and R H Burris, *University of Wisconsin, Madison*

The relation of boron to certain plant oxidases

- 5 L D Abbott, Jr (*introduced by J D Forbes*), *Medical College of Virginia, Richmond*

Determination of phenolsulfatase activity

- 6 Frederick G Smith (*by invitation*), Willard B Robinson (*by invitation*), and Elmer Stotz, *Cornell University, Geneva, N Y State Agricultural Expt Station*

Colorimetric method for determination of phenol oxidase and peroxidase in plant tissues

- 7 Marian W Kies (*introduced by A K Balls*), *U S Department of Agriculture, Albany, Calif*

Complex nature of soybean lipoxidase

- 8 B Axelrod (*introduced by A K Balls*), *U S Department of Agriculture, Albany, Calif*

A new enzymatic phosphate transfer

## BIOCHEMISTRY B

Thursday, 2 00 p m

PRIVATE DINING ROOM 2, STEVENS HOTEL

### Disease

- 1 Evelyn B Man, Charles Culotta (*by invitation*), Dorothy Siegfried (*by invitation*),

and Carter Stilson (*by invitation*), *Yale University School of Medicine, New Haven, Conn*

Serum precipitable iodines in recognition of cretinism and in control of thyroid medication

- 2 J F McClendon and Wm C Foster (*by invitation*), *Hahnemann Medical College, Philadelphia*

On the mechanism of the anomalous action of iodine in lowering the basal metabolic rate

- 3 Emil J Baumann and Nannette Metzger (*by invitation*), *Montefiore Hospital, New York*

Action of thiocyanates in producing goiter

- 4 John P Hummel (*introduced by H A Mattill*), *State University of Iowa, Iowa City*

A defect in oxidative phosphorylation in nutritional muscular dystrophy

- 5 Stanley R Ames (*introduced by Philip L Harris*), *Distillation Products, Inc, Rochester, N Y*

Effect of calcium on the inhibition of the succinic oxidase system by alpha-tocopheryl phosphate

- 6 Walter D Block, Naomi Geib (*by invitation*), and William D Robinson (*by invitation*), *University of Michigan, Ann Arbor*

Influence of sulfhydryl groups on oxygen consumption of tissues in the presence of gold compounds

- 7 Bernard J Jandorf, Evan Calkins (*by invitation*), and Abraham Goldin (*by invitation*), *Edgewood Arsenal, Maryland*

Metabolic effects of a nitrogen mustard on mouse sarcoma 180

- 8 Carl S Vestling, Richard E Maxwell (*by invitation*), Jesse N Williams, Jr (*by invitation*), and Henry Quastier (*by invitation*), *University of Illinois and Carle Hospital, Urbana*

Further studies of the enzymes of normal and leucemic mouse liver homogenates

- 9 Ella H Fishberg and Virginia Rechnittzer (*by invitation*), *Beth Israel Hospital, New York*

Excretion of benzoquinone acetic acid in acute rheumatic fever

- 10 Sam Scifter, David M Harkness (*by invitation*), Edward Muntwyler, and Joseph Seifter, *Long Island College of Medicine, Brooklyn and Weyth Institute of Applied Biochemistry, Philadelphia*

Chemical studies on blood and muscle from rabbits and rats paralyzed by dithiobisuracil

- 11 Otto Rosenthal, *University of Pennsylvania, Philadelphia*

The metabolism of the mucosa of the small intestine

- 12 Maurice M Black (*by invitation*) and Israel



S Kleiner, *New York Medical College and Brooklyn Cancer Institute*

The selective inhibition of active phosphate bond metabolism in human malignant cells

### BIOCHEMISTRY C

Thursday, 2 00 p m

WEST BALLROOM, STEVENS HOTEL

#### Proteins (continued)

- 1 Sidney F Velick and Ethel Ronzoni, *Washington University Medical School, St Louis*  
The amino acid composition of d-glyceraldehydephosphate dehydrogenase and aldolase from rabbit skeletal muscle
- 2 Anne Beloff (by invitation) and Christian B Anfinsen, *Harvard Medical School, Boston*  
The products of proteolysis of some purified proteins
- 3 Richard Winzler, Arthur W Devor (by invitation), and John W Mehl, *University of Southern California School of Medicine, Los Angeles*  
A mucolipoprotein in normal human plasma
- 4 Earl R Norris and James C Mathies (by invitation), *University of Washington, Seattle*  
The gastric proteinase of yellow fin tuna (*Neothunnus macropterus*)
- 5 T L McMeekin, E Ella Monica (by invitation), and J H Custer (by invitation), *Eastern Regional Research Laboratory, Philadelphia*  
Separation and properties of bovine whey proteins
- William G Gordon and William F Semmett (by invitation), Robert S Cable (by invitation), and David G Doherty (by invitation), *Eastern Regional Research Laboratory, Philadelphia*  
Some amino acid analyses of whole casein, alpha-casein and beta casein
- 7 Dennis T Mayer and Lloyd E Thomas (introduced by A G Hogan), *University of Missouri, Columbia*  
The proteins of mammalian spermatozoa
- 8 Elizabeth L Knapp (by invitation) and Joseph I Routh, *State University of Iowa, Iowa City*  
Electrophoretic patterns of plasma from normal and sick children
- 9 Stephan Ludewig, Alfred Chanutin, and Erland C Gjessing (by invitation), *University of Virginia, Richmond*  
Fractionation studies of the plasma proteins of control and injured rats
- 10 Erland C Gjessing (by invitation) and Alfred Chanutin, *University of Virginia, Richmond*

Fractionation studies of the serum proteins of control and injured goats

### BIOCHEMISTRY

#### Papers Read by Title

- 1 H A Abramson, *Mt Sinai Hospital, New York*  
Vitamin C aerosol for inhalation therapy of the lungs
- 2 Marie A Andersch and C Jelleff Carr, *University of Maryland and University Hospital, Baltimore*  
The effect of alloxan on the level of serum amylase of the rat
- 3 James C Andrews and Enrique Herrarte (by invitation), *University of North Carolina, Chapel Hill*  
Enzymic hydrolysis of phytin by pure bacterial cultures
- 4 W D Armstrong and Haydee Estremera (by invitation), *University of Minnesota, Minneapolis*  
Effect of protein deficient diets on the skeleton of the mature rat
- 5 Paul Bartlett (by invitation) and Oliver H Gaebler, *Henry Ford Hospital, Detroit*  
Dextrose Nitrogen ratios in pyridoxine deficiency
- 6 Howard H Beard, *The Chicago Medical School*  
Effect of large doses of Jaffe reactive substances upon urinary excretion of nitrogenous constituents
- 7 Howard H Beard, *The Chicago Medical School*  
Some observations upon the nature and distribution of Jaffe reactive material in beef liver
- 8 Howard H Beard, *The Chicago Medical School*  
The comparative metabolism of Jaffe reactive substances in the rat
- 9 Howard H Beard, *The Chicago Medical School*  
The production of creatine-creatinine destroying enzymes from human urine and gastric juice
- 10 Maurice Black (introduced by Israel S Kleiner), *New York Medical College and Brooklyn Cancer Institute*  
Diagnostic changes in the reducing power of plasma in malignant neoplasia and therapeutic implications
- 11 Donald E Bowman, *Indiana University School of Medicine, Indianapolis*  
Acceleration of blood coagulation by iodinated trypsin
- 12 Philip P Cohen and LeMar F Remmert (by invitation), *University of Wisconsin, Madison*  
Partial purification of a proteolytic enzyme from human serum

- 13 H R Crookshank (by invitation) and Emmett B Carmichael, *Medical College of Alabama, Birmingham*  
Nitrogen content of three foreign proteins (toxins)
- 14 Frank A Csonka and M W Olson (by invitation), *United States Department of Agriculture, Beltsville, Md*  
Utilization of amino acids by the chicken embryo
- 15 K P Dimiek (by invitation), G Alderton (by invitation), H D Lighthody, and H L Ferold (by invitation), *Western Regional Research Laboratory, Albany, Calif*  
A method for purification of subtilin
- 16 Zacharias Dische, *Columbia University, New York*  
New characteristic color reactions of carbohydrates with SH compounds in  $H_2SO_4$
- 17 Zacharias Dische, *Columbia University, New York*  
Specific color reactions of glucuronic and galacturonic acids
- 18 Robert L Dryer (by invitation), W D Paul (by invitation), and Joseph I Routh, *State University of Iowa, Iowa City*  
The influence of acetylsalicylic acid ingestion on the electrophoretic patterns of plasma
- 19 J C Forbes and Olga Petterson, *Medical College of Virginia, Richmond*  
A study of the possible hypotropic action of a dried stomach preparation
- 20 H Fraenkel-Conrat and H S Oleott, *Western Regional Research Laboratory, Albany, Calif*  
Possible cyclic structure of salmine
- 21 Jose M Gonalves (by invitation), Vincent E Price (by invitation), Maurice Errera (by invitation) and Jesse P Greenstein, *National Institute of Health, Bethesda, Md*  
Desamidation of amides in the presence of pyruvate
- 22 David M Greenberg, Jane Fraenkel-Conrat (by invitation), and Mary Beth Glendening (by invitation), *University of California Medical School, Berkeley*  
Studies with radioactive phosphorus of acid-soluble phosphate changes in hyperthyroidism
- 23 Robert Houston Hamilton, (introduced by Howard W Robinson), *Temple University School of Medicine, Philadelphia*  
Photometric determination of bromsulphalein in hemolyzed, lipemic, or icteric serum
- 24 John Hearon (introduced by Dean Burk), *National Institute of Health, Bethesda, Md*  
The configuration of oxy-bis 9 cobaltodihistidine
- 25 John Hearon (introduced by Dean Burk), *National Institute of Health, Bethesda, Md*  
The tetrahedral configuration of cobaltodihistidine
- 26 Elmore Holmes (by invitation) and Dempsey B Morrison, *University of Tennessee, Memphis*  
Separation and electrophoretic analyses of the proteins of normal dog tissues
- 27 Harold A Jeskey (by invitation) and Dempsey B Morrison, *University of Tennessee, Memphis*  
Effect of fever therapy on the electrophoresis pattern of plasma proteins
- 28 R Norman Jones (by invitation) and Konrad Dobriner, *Memorial Hospital and National Research Council of Canada*  
The location of the position of carbonyl groups in ketosteroids by infrared spectrography
- 29 Paul H Kopper (by invitation) and Howard H Beard, *The Chicago Medical School, Chicago*  
Creatinase activity of a strain of pseudomonas
- 30 H O Kunkel (by invitation) and P B Pearson, *A and M College of Texas, College Station*  
A rapid photoelectric method for the determination of serum magnesium
- 31 J C Lewis and Eugene F Jansen (by invitation), *Western Regional Research Laboratory, Albany, Calif*  
Enhancement of subtilin activity by methylation
- 32 Hans Lineweaver, Herman J Morris (by invitation), Leo Kline (by invitation), and R S Bean (by invitation), *Western Regional Research Laboratory, Albany, Calif*  
Enzymes of fresh infertile hen eggs
- 33 Colin C Lucas (by invitation), Jessie H Ridout (by invitation), Jean M Patterson (by invitation), and C H Best, *University of Toronto, Canada*  
Quantitative hypotropic studies
- 34 Dempsey B Morrison, Edward H Bloek (by invitation), and Harold A Jeskey (by invitation), *University of Tennessee, Memphis*  
Changes in the electrophoretic pattern of the plasma proteins of monkeys (*Macaca mulatta*) with infections
- 35 Evangeline Papageorge and Foster Adair (introduced by Howard B Lewis), *Emory University, Atlanta, Ga*  
Blood levels of certain constituents in normal adults before and after ingestion of rutin
- 36 Edith Sims (by invitation) and John R Totter, *University of Arkansas, Little Rock*  
The inhibition of conjugase by a polypeptide of *p* aminobenzoic acid
- 37 Morris Soodak (by invitation) and Leopold R Cerecedo, *Fordham University, New York*

- The effect of oxythiamine and some oxythiamine derivatives on mice
- 38 M Spiegel-Adolf, P H Wilcox (*by invitation*), and E Spiegel (*by invitation*), *State Hospital, Traverse City, Mich., and Temple University School of Medicine, Philadelphia*  
Enzymatic action of the cerebrospinal fluid following electrically induced convulsions
- 39 Mona Spiegel-Adolf, *Temple University School of Medicine, Philadelphia*  
Physicochemical studies on water soluble chlorophyll derivatives
- 40 M Spiegel-Adolf, P H Wilcox (*by invitation*), and E A Spiegel (*by invitation*), *Traverse City State Hospital, Mich., and Temple University School of Medicine, Philadelphia*
- Spectrophotometry of the cerebrospinal fluid before and after electrically induced convulsions
- 41 Jakob A Stekol, *Amino Products, Rossford*  
A study on the availability of beta-methoxypropanol for growth purposes in the rat
- 42 Claude A Villee (*introduced by A Baird Hastings*), *Harvard Medical School, Boston*  
Investigations of the growth metabolism of normal and mutant imaginal discs of insects
- 43 Robert F Witter (*by invitation*) and Elmer Stoltz, *Cornell University, N Y State Agricultural Experimental Station, Geneva*  
Colorimetric determinations of  $\beta$ -diketones and triacetic lactone (6 methyl pyranone)

## THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

### THIRTY-SEVENTH ANNUAL MEETING

#### PHARMACOLOGY A

Monday, 9 00 a m

UPPER TOWER ROOM—STEVENS HOTEL

#### Sympathetic and Related Drugs

- William A Wolff and Marina A Hawkins (*introduced by Harold D Green*), *Tobacco Research Laboratory, Bowman Gray School of Medicine, Winston-Salem, N C*  
The relation of blood nicotine levels to type of smoking
- 2 J K Finnegan (*by invitation*), P S Larson, and H B Haag, *Department of Pharmacology, Medical College of Virginia, Richmond*  
Observations on the role of nicotine in cigarette smoke irritation
- 3 P S Larson, J K Finnegan (*by invitation*), and H B Haag, *Department of Pharmacology, Medical College of Virginia, Richmond*  
Observations on the relation of dose of nicotine administered to the percentage excreted unchanged
- 4 Betty L Bertcher (*by invitation*) and W J R Camp, *Dept of Pharmacology, University of Illinois College of Medicine, Chicago 12*  
Neosynephrine bradycardia
- 5 D M Green, *School of Medicine, University of Washington*  
Responses to benzedrine sulfate—1,467 cases
- 6 E William Ligon, Jr, Rollan Swanson, and E Leong Way (*introduced by Paul K Smith*), *Department of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
Excretion of octin, a sympathomimetic aliphatic amine
- 7 F E Shaffer (*introduced by P K Knoefel*), *University of Louisville*  
A study of 2-methylaminoheptane
- 8 Earl R Loew, Audrey Micetich (*by invitation*), and Paul Achenbach (*by invitation*), *Dept of Pharmacology, University of Illinois College of Medicine, Chicago 12, Illinois*  
Antagonism of the excitatory responses to epinephrine and adrenergic nerve stimulation with benzhydryl-alkyl- $\beta$ -chloroethyl amines
- 9 Mark Nickerson (*introduced by Louis S Goodman*), *Dept of Pharmacology, University of Utah School of Medicine, Salt Lake City, Utah*  
Site of the adrenergic blocking action of dibenamine
- 10 Theodore O King (*introduced by T Koppányi*), *Dept of Pharmacology and Materia Medica, Georgetown University, School of Medicine*

- A comparative study of sympatholytic drugs
- 11 F A Marzoni (*by invitation*), M J Reardon (*by invitation*), and James P Hendrix, *Depts of Surgery and Medicine, Duke University School of Medicine, Durham, N C*  
The effects of benzyl-imidazoline (Priscol) in partially sympathectomized dogs
  - 12 James P Hendrix, M J Reardon (*by invitation*), and F A Marzoni (*by invitation*), *Depts of Medicine and Surgery, Duke University School of Medicine, Durham, N C*  
Observations on the effects of benzyl-imidazoline (Priscol) in man
  - 13 A M Lands, V L Nash (*by invitation*), H M McCarthy (*by invitation*), and B L Dertinger (*by invitation*), *Pharmacological Research Laboratory, Frederick Stearns & Co, Detroit*  
Sympathin I—Mimetic action of N alkyl analogues of epinephrine (Physiol)
  - 14 O H Siegmund (*by invitation*), H R Granger (*by invitation*), and A M Lands, *Pharmacological Research Laboratory, Frederick Stearns & Co, Detroit*  
Bronchodilator action of some N alkyl analogues of epinephrine

## PHARMACOLOGY B

Monday, 9 00 a m

LOWER TOWER ROOM—STEVENS HOTEL

## Cardiac and Related Drugs

- 1 Albert Wollenberger (*introduced by Otto Krayser*), *Dept of Pharmacology, Harvard Medical School*  
Influence of cardiac glycosides on respiration and glycolysis of heart muscle and brain cortex
- 2 Anthony M Ambrose and Floyd DeEds, *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U S Department of Agriculture, Albany, California*  
The protective action of rutin against capillary injury
- 3 Joseph H Hafkenschiel and James E Eckenhoff (*introduced by Carl F Schmidt*), *Dept of Pharmacology and Harrison Department of Surgical Research, University of Pennsylvania, and Department of Anesthesiology, Hospital of the Univ of Pennsylvania, Philadelphia*  
Effect of five drugs on coronary blood flow in the dog
- 4 A Farah and G Maresh (*introduced by Otto Krayser*), *Department of Pharmacology, Harvard Medical School, Boston, Mass*  
Influence of rate of administration on therapeutic

- the irregularity, and lethal dose of some cardiac glycosides
- 5 John C Krantz, Jr and Frederick K Bell (*by invitation*), *University of Maryland School of Medicine*  
The Baljet reaction and the glycosides of digitalis
  - 6 Harry Gold, Walter Modell, and McKeen Cattell, *Dept of Pharmacology, Cornell University Medical College, and Cardiac Services of Beth Israel Hospital and Hospital for Joint Diseases, New York*  
Convulsant and cardiac actions of red squill
  - 7 Walter Modell, Morris Pearlmutter (*by invitation*), and Donald A Clarke (*by invitation*), *Dept of Pharmacology, Cornell University Medical College, and Cardiac Services of Beth Israel Hospital and Hospital for Joint Diseases, New York*  
Relative importance of digitalis and mercurial diuretics in the treatment of advanced heart failure
  - 8 H A Braun and L M Lusky (*by invitation*), *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C*  
A comparative study of the intravenous cat and intravenous pigeon methods for digitalis assay
  - 9 Wallace F White (*by invitation*), Julius Belford (*by invitation*), and William T Salter, *Laboratory of Pharmacology and Toxicology, Yale University School of Medicine New Haven, Connecticut*  
A comparison of the inotropic effect of cardiac glycosides on isolated mammalian heart muscle
  - 10 Russell A Waud and Gwendolyn Pearson Kirk (*by invitation*), *Department of Pharmacology, University of Western Ontario, London, Canada*  
A cardiac action of tannins
  - 11 G H Acheson, Alfred Farah (*by invitation*), and Gordon N French (*by invitation*), *Dept of Pharmacology, Harvard Medical School, Boston, Mass*  
Some effects of dibenamine on the mammalian heart
  - 12 Theodore R Sherrod (*by invitation*) and W J R Camp, *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12*  
The effects of digitalis on electrolytes of heart muscle
  - 13 Byrl E Benton (*by invitation*) and W J R Camp, *Dept of Pharmacology, University of Illinois College of Medicine, Chicago 12*  
A study of the effect of digitoxin on blood oxygen
  - 14 R P Walton and O J Brodie (*by invitation*),

*Dept of Pharmacology, Medical College of South Carolina*

Effect of drugs on myocardial contraction force as measured under conditions of an intact circulation

## JOINT SESSION OF THE FEDERATION

*Monday, 1 45 p m*

GRAND BALLROOM, STEVENS HOTEL

Program on p 3

## PHARMACOLOGICAL SOCIETY BUSINESS MEETING

*Monday, 4 15 p m*

UPPER TOWER ROOM—STEVENS HOTEL

### MOTION PICTURES

*Monday, 7 00-11 00 p m*

UPPER TOWER ROOM—STEVENS HOTEL

(For program see p 3)

### PHARMACOLOGY A

*Tuesday, 9 00 a m*

UPPER TOWER ROOM—STEVENS HOTEL

### Parasympathetic Drugs, DFP, etc

- 1 I F Stein, Jr (*by invitation*), F Steigmann, and Karl A Meyer (*by invitation*), *Cook County Hospital and Hektoen Institute for Medical Research*

Studies of gastric motility on ulcer patients before and after vagotomy—effect of parasympathomimetic drugs

- 2 James Y P Chen (*by invitation*) and Benedict E Abreu, *Division of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco*

Certain pharmacologic effects of  $\beta$ -piperidinoethyl phenyl- $\alpha$ -thienylglycolate

- 3 Ralph W Brauer, Harold C Hodge, and Herbert A Ravin (*introduced by Otto Kraye*), *Dept of Pharmacology, Harvard Medical School, and Dept of Pharmacology and Toxicology, School of Medicine and Dentistry, The Univ of Rochester, Rochester, New York*

The inhibition of the cholinesterase activity of human and canine blood plasma and erythrocytes by certain phosphate esters

- 4 Ernest C Hagan and Geoffrey Woodard (*introduced by Bert J Vos*), *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C*

Toxicological properties of hexacthyl tetra phosphate

- 5 George H Mangun (*by invitation*) and Kenneth P DuBois, *Univ of Chicago Toxicity Laboratory and the Depts of Biochemistry and Pharmacology, University of Chicago*

Toxicity and mechanism of action of tetraethyl pyrophosphate

- 6 Dorothea Starbuck Miller and Benson Ginsburg (*introduced by E M K Geiling*), *Toxicity Laboratory and College, University of Chicago*

Site and mode of action of several cholinesterase inhibitors

- 7 Amedeo S Marrazzi and Norman E Jarvik (*by invitation*), *Wayne University College of Medicine*

The differential effects on synaptic transmission and nerve conduction of di-isopropyl fluorophosphate (DFP) and atropine

- 8 Frederick Sperling (*by invitation*), Alexander G Karczmar (*by invitation*), Theodore O King (*by invitation*), and Theodore Koppányi, *Dept of Pharmacology and Materia Medica, Georgetown University, School of Medicine*

The effects of di-isopropyl fluorophosphate and physostigmine on the sympathetic ganglia

- 9 Carlton C Hunt and Walter F Riker, Jr (*introduced by McKen Cattell*), *Dept of Pharmacology, Cornell University Medical College, New York*

Studies on chronic poisoning by di-isopropyl fluorophosphate in cats

- 10 W Clarke Wescoe, 1st Lt, M C (*by invitation*), Ray E Green, 1st Lt, M C (*by invitation*), Bernard P McNamara (*by invitation*), and Stephen Krop, *Pharmacology Section, Medical Division, Edgewood Arsenal, Maryland*

The influence of atropine on the central effects of di-isopropyl fluorophosphate (DFP) in experimental animals

- 11 R E Green, 1st Lt, M C (*by invitation*), Elizabeth A McKay (*by invitation*), and Stephen Krop, *Pharmacology Section, Edgewood Arsenal, Maryland*

The action of di-isopropylfluorophosphate on the caliber of the bronchial tree in isolated lungs

- 12 Harold F Chase, John L Schmidt (*by invitation*), and Ban K Bhattacharya (*by invitation*), *Dept of Pharmacology and Division of Anesthesia, of the Dept of Surgery, School of Medicine, Western Reserve University and University Hospitals of Cleveland*
- Antagonism of curare action by di-isopropylfluorophosphate (DFP)

- 13 Klaus R Unna and Kazuo K Kimura (*by invitation*), *Dept of Pharmacology, University of Illinois College of Medicine, Chicago 12, Illinois*

Antagonism between curare and physostigmine

- 14 Clara Torda and Harold G Wolff, *New York Hospital and Depts of Medicine (Neurology) and Psychiatry, Cornell University Medical College, New York, New York*

Effect of toxins of clostridium botulinum and clostridium tetani on acetylcholine synthesis

- 15 Sydney Ellis (*by invitation*), Shirley Sanders (*by invitation*), and Oscar Bodansky, *Biochemistry Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Maryland*

Carbon tetrachloride liver damage and acetylcholine esterase activity in the rabbit and rat

## PHARMACOLOGY B

Tuesday, 9 00 a m

LOWER TOWER ROOM—STEVENS HOTEL

### Metabolism and Drugs

- 1 R A Simpson (*introduced by O S Orth*), *Dept of Anesthesiology, State of Wisconsin General Hospital, Madison*

A laboratory investigation of intravenous oxygen therapy

- 2 Allan L Lorincz and J J Jacoby (*introduced by J M Coon*), *Dept of Pharmacology, The University of Chicago*

Studies on the perenteral administration of hydrogen peroxide

- 3 H R Hulpieu and V V Cole, *Dept of Pharmacology, Indiana University School of Medicine, Indianapolis*

Rate of alcohol metabolism not affected by pyruvate or arsenite

- 4 Walter M Booker, David M French, and Pedro A Molano (*introduced by A H Maloney*), *Dept of Pharmacology, Howard University School of Medicine*

Further observations on the effect of prolonged pentothal on metabolism of carbohydrates and of proteins

- 5 G A Emerson, P L Ewing, and (*by invitation*) Thurlie B Thomas, *Dept of Pharmacology, Univ of Texas Medical Branch, Galveston, and Dept of Zoological Sciences, Carleton College, Northfield, Minnesota*

Alloxan diabetes in thymectomized rats

- 6 Chalmers L Gemmill, *Dept of Pharmacology, School of Medicine, University of Virginia*

Effect of theobromine derivatives and alloxan on muscle metabolism

- 7 Norman A David and F Bertram Zener (*by invitation*), *Dept of Pharmacology, University of Oregon Medical School, Portland, Oregon*

Influence of iodine therapy on blood iodine and basal metabolic rate in pregnancy

- 8 Douglas S Riggs (*introduced by Otto Krayner*), *Laboratory of the Fairfield State Hospital, Newtown, Connecticut*

The response of patients with thiouracil-induced myxedema to desiccated thyroid

- 9 Arthur E Meyer and Jean P McEwen (*introduced by Arthur A Hellbaum*), *The Mallinckrodt Therapeutic Foundation, Brooklyn, N Y*

A protein-free fraction from desiccated thyroid substance of physiologic action

- 10 Joseph Seifter, *Wyeth Institute of Applied Biochemistry, Philadelphia, Pennsylvania*

Prolonged administration of goitrogenic compounds to dogs

- 11 A J Bergmann (*by invitation*), S Archer (*by invitation*), J O Hoppe (*by invitation*), and T J Becker, *Sterling-Winthrop Research Institute, Roseland, New York*

The antithyroid activity of some 6 substituted-2 thiouracils

## PHARMACOLOGY C

Tuesday, 9 00 a m

ENGLISH WALNUT ROOM—CONGRESS HOTEL

### Anesthetics and Barbiturates

- 1 Janet Travell and Audrie L Bobb (*by invitation*), *Dept of Pharmacology, Cornell University Medical College, N Y*

Mechanism of relief of pain in sprains by local injection techniques

- 2 Elizabeth H Jenney (*by invitation*), and Carl C Pfeiffer, *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12*

The use of local skin temperature responses to evaluate the histamine-like effect of "Pontocaine" (Tetracaine, U S P)

- 3 R B Forney (*by invitation*), H R Hulpieu, and V V Cole, *Dept of Biochemistry and Pharmacology, Indiana University School of Medicine, Indianapolis*

Procaine studies in tissue applying the Bratton-Marshall method for the determination of sulfonamides

- 4 Nellie Perry Watts (*introduced by Carl A Dragstedt*), *Dept of Pharmacology, Abbott Research Laboratories, North Chicago, Illinois*

Some factors affecting duration of action of local anesthetics when injected intracutaneously in guinea pigs

- 5 C Jelleff Carr, *Department of Pharmacology, School of Medicine, University of Maryland*  
The anesthetic properties of three isomeric ethers

- 6 J L Svrbely, W C Alford (by invitation), & W F. von Oettingen, *Industrial Hygiene Research Laboratory, National Institute of Health, Bethesda, Maryland*

Toxicity and narcotic action of mono-chloro-mono-bromo-methane with special reference to inorganic and volatile bromide in blood, urine, and brain

- 7 J J Jacoby (by invitation), H M Livingstone (by invitation), and E M K Geiling, *The Departments of Surgery and Pharmacology, the University of Chicago*

Intravenous administration of gaseous anesthetics

- 8 Ewart A Swinyard (introduced by Louis S Goodman), *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City, Utah*

Validity of laboratory anticonvulsant tests for predicting antiepileptic potency and specificity

- 9 Milton T Bush and Thomas C Butler, *Vanderbilt Univ School of Medicine*

Metabolic fate of thiobarbital

- 10 J B Wyngaarden (by invitation), L A Woods (by invitation), R Ridley (by invitation), and M H Seevers, *Dept of Pharmacology, Univ of Michigan*

Anesthetic properties of several thiobarbiturates in dogs

- 11 A R Kelly (by invitation), B J Adams (by invitation), and F E Shideman, *Dept of Pharmacology, University of Michigan*

The role of the liver in the detoxication of thiopental (Pentothal) and certain other thiobarbiturates

- 12 Kazuo K Kimura (by invitation) and Klaus R Unna, *Dept of Pharmacology, Illinois College of Medicine, Chicago 12*

The effect of a non-curarizing dose of d-tubocurarine on the increased motor activity in mice induced by barbiturates

- 13 E Ross Hart and O M Weaver, Jr, (by invitation), *Dept of Pharmacology, Jefferson Medical College of Philadelphia*

Analgesia in rats as a result of administration of barbiturates, and its relation to hypnosis

- 14 R K Richards, *Department of Pharmacology, Abbott Laboratories, North Chicago, Ill*  
Experiments on the inactivation of pentothal (Physiol )

## STATIC DEMONSTRATIONS

Tuesday, 2 00-10 00 p m

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE

(For program see p 3 )

### PHARMACOLOGY A

Tuesday, 2 00 p m

PARLORS A, B AND C—CONGRESS HOTEL

### Joint Session, Biometrics Section, American Statistical Association, and the Pharmacological Society

- 1 W A Crandall and Muriel M Burr (introduced by L I Pugsley), *Food and Drugs Divisions, Department National Health and Welfare, Ottawa, Canada*

Precision of microbiological assays for riboflavin, niacin and pantothenic acid (Biochem )

- 2 Walther H Ott (introduced by Hans Molitor), *Merck Institute for Therapeutic Research, Rahway, N J*

A quantitative assay method for pyrogens

- 3 D M Young and R G Romans (introduced by E W McHenry), *Connaught Medical Research Laboratories, University of Toronto*

One blood sample per rabbit per test day in the assay of insulin (Biochem )

- 4 Helen M Tepperman (by invitation), Maurice V L'Heureux (by invitation), and Alfred E. Wilhelm, *Department of Physiological Chemistry, Yale University, New Haven, Conn*

Estimation of parathyroid hormone activity by its effect on serum inorganic phosphorus in the rat (Biochem )

- 5 Ralph I Dorfman, *Departments of Biochemistry and Medicine, Western Reserve University School of Medicine and Lakeside Hospital, Cleveland 6, Ohio*

The bioassay of various hormones using a simplified experimental design (Biochem )

- 6 C I Bliss and Elmer L Sevringhaus (by invitation), *Connecticut Agricultural Experiment Station and Scientific Department, Hoffmann-La Roche, Inc, Nutley, N J*

A collaborative study of methods for assaying analgesic drugs

### PHARMACOLOGY B

Tuesday, 2 00 p m

PINE ROOM—CONGRESS HOTEL

- 1 Morris Belkin (by invitation), (introduced by R P Walton), *Dept of Pharmacology, Medical College of South Carolina, Charleston*

- Effect of podophyllin on transplanted mouse tumors
- 2 K G Wakim and K K Chen, *Indiana University Medical Center, and the Lilly Research Laboratories, Indianapolis*  
The action of alstonine
  - 3 E L McCawley, A Mauro (by invitation), and R G Grenell, *Laboratories of Pharmacology and Neuro-Anatomy, Yale Univ School of Medicine, New Haven, Connecticut*  
A method for simultaneous recording of pharmacological and physiological data
  - 4 S Anderson Peoples, Don W Chapman (by invitation), and H F Arnold (by invitation), *Dept of Physiology and Pharmacology, and Dept of Medicine, Baylor University College of Medicine, Houston, Texas*  
Sulfathiazole clearance as a measure of glomerular filtration rate
  - 5 Kurt Salomon, Thomas Thale, and Beverly Wescott Gabrio, *University of Rochester, School of Medicine and Dentistry, Rochester, New York*  
Investigation of the psycho chemical basis of visual hallucinations produced by mescaline
  - 6 Walter E Barrett (introduced by Fredrick F Yonkman), *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, New Jersey*  
A method of studying eiliary motility by direct observation
  - 7 Theodore Koppanyi and Alexander G Karezmar (by invitation), *Dept of Pharmacology and Materia Medica, Georgetown Univ School of Medicine*  
Pharmacological methods in the study of overt behavior
  - 8 R H K Foster and A J Begany (by invitation), *Dept of Pharmacology, St Louis University School of Medicine*  
Some factors concerned in the assay of heparin
  - 9 Frederiek Bernheim, *Duke Medical School*  
The specificity of hydantoinase (Biochem)
  - 10 R N Harger, and (by invitation), J R Bennet, H R Hulpieu and A J Schneider, *Depts of Biochemistry, Pharmacology and Pathology, Indiana Univ School of Medicine, Indianapolis*  
Tissue storage of mercury following repeated administration of organic mercury diuretics or mercuric chloride (Biochem)
- George Sprague, Jr (introduced by H B Haag), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York*  
Toxicity of uranium dusts
- 2 Charles W LaBelle (introduced by H B Haag), *The Division of Pharmacology and Toxicology, Department of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, N Y*  
The variation of toxicity with particle size of  $UO_2$  dust
  - 3 Sidney Lashin (introduced by H B Haag), *Division of Pharmacology and Toxicology, Department of Radiology, School of Medicine and Dentistry, The University of Rochester, Rochester, N Y*  
Vacuum coating with selenium metal as a method of producing a high refractive index medium for particle-size measurements
  - 4 Elliott A Maynard, Challiss Randall, and Harold C Hodge (introduced by H B Haag), *Division of Pharmacology and Toxicology, Department of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, N Y*  
Effects of feeding uranium nitrate in the diets of breeding white rats
  - 5 William F Neuman, R W Fleming, A B Carlson J O'Leary, P O'Connell and B J Mulryan (introduced by H B Haag), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York*  
The distribution and excretion of uranium following intravenous injection
  - 6 J H Wills and E Main (introduced by Raymond N Bieter), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, N Y*  
Renal effects of uranium
  - 7 Alexander Dounce (introduced by Raymond N Bieter), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, N Y*  
Catalasuria as a sensitive test for uranium poisoning
  - 8 A Rothstein, D Dittman, H Berke, and J T Minor (introduced by Raymond N Bieter), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, New York*  
The excretion and retention of nonprotein nitrogen (NPN) in animals poisoned with uranium

## PHARMACOLOGY C

Tuesday, 2 00 p m

ENGLISH WALNUT ROOM—CONGRESS HOTEL

### Pharmacology of Uranium

- 1 H E Stokinger, Eugene Roberts, Charles J Spiegl, A Rothstein, J J Rothermel,



- 9 Eugene Roberts & Charles Bishop (*introduced by Raymond N Bieter*), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, N Y*

Certain aspects of carbohydrate metabolism in normal animals and in animals poisoned with U-nitrate, U-chloride and allovan

- 10 Frances L Haven and Chalhss Randall (*introduced by R N Bieter*), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, New York*  
The urinary excretion of citric acid in uranium poisoning

- 11 Harold C Hodge, Alexander Dounce, J H Wills, T H Lan, Paul Fanta, G H Tishkoff (*introduced by Raymond N Bieter*), *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, University of Rochester, Rochester, N Y*  
Mechanism of uranium poisoning

## PHARMACOLOGY A

Wednesday, 9 00 a m

PARLORS A, B C—CONGRESS HOTEL

### Chemotherapeutic Agents

- 1 Raymond N Bieter, Ashton C Cuckler (*by invitation*), John T Litchfield, Jr, Theresa E Brey (*by invitation*), and Harold N Wright, *Dept of Pharmacology, Univ of Minnesota Medical School, Minneapolis, Minnesota*

Chemotherapy of cotton rat filariasis with certain antimony and arsenic compounds

- 2 Elizabeth M Cranston, Ashton C Cuckler (*by invitation*), John T Litchfield, Jr, Theresa Brey (*by invitation*), Harold N Wright, and Raymond N Bieter, *Dept of Pharmacology, University of Minnesota Medical School, Minneapolis, Minnesota*

Chemotherapeutic activity of cyanines and related compounds in filariasis in the cotton rat

- 3 Harold N Wright, Ashton C Cuckler (*by invitation*), Elizabeth M Cranston and Raymond N Bieter, *Dept of Pharmacology, University of Minnesota Medical School, Minneapolis, Minnesota*

Pharmacology of 1,1'-di  $\beta$  ethoxyethyl-2,2' carbocyanine p-toluene sulfonate and derivatives in cotton rat filariasis

- 4 Arnold D Welch, Lawrence Peters, Ernest Bueding, Arthur D Valk (*by invitation*), and Aeme Higashi (*by invitation*), *Dept of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio*

Studies on the relative antifilarial activity of a series of cyanine dyes against *litomosoides carini*

- 5 Ernest Bueding, *Department of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio*

Effect of cyanine dyes and of sodium fluoracetate on the metabolism of filariae (*L. carini*) (*Biochem*)

- 6 Lawrence Peters, Aeme Higashi (*by invitation*) and Arnold D Welch, *Dept of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio*

Investigation of 1-ethyl-3,6 dimethyl 2 phenyl-4-pyrimido-2-cyanine chloride (CMR No 863) for possible therapeutic utility in human filariasis

- 7 Arthur D Valk, Jr (*by invitation*), Lawrence Peters, and Arnold D Welch, *Dept of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio*

Some observations on distribution and excretion of 1-ethyl-3,6-dimethyl-2-phenyl-4 pyrimido-2 cyanine chloride (CMR #863) in dogs

- 8 Robert E Smith, Lt Commander, HS, USNR (*introduced by B G King*), *Naval Medical Research Institute*

Studies on the biological exchange of radio antimony in animals and man (*Physiol*)

- 9 Maxwell Schubert and Arthur C DeGraff, *Department of Therapeutics and Laboratory of Experimental Therapeutics, New York University, College of Medicine, New York, N Y*

Experimental chemotherapy of schistosomiasis 1 Methods and conditions for drug testing

- 10 Arthur C DeGraff and Maxwell Schubert, *Department of Therapeutics and Laboratory of Experimental Therapeutics, New York University, College of Medicine, New York, New York, N Y*

Experimental Chemotherapy of schistosomiasis 2 Comparison of effects of specific drugs

- 11 F W Schueler, *Department of Pharmacology, University of Chicago* (*introduced by E M K Geiling*)

Studies on the mechanism of drug resistance in trypanosomes

- 12 Etta Mae MacDonald (*introduced by A L Tatum*), *Dept of Pharmacology, Univ of Wisconsin Medical School, Madison*

Action of chemotherapeutic agents on *trichomonas vaginalis*, *trichomonas hominis* and *trichomonas foetus* in vitro

- 13 Elizabeth Taylor (*by invitation*), Fred H Snyder (*by invitation*) and Fred W Oberst,

*Dept of Biochemistry, Research Laboratories, The W S Merrell Co, Cincinnati*

The excretion of sulfamidamide derivatives after oral administration to white rats (Biochem)

## PHARMACOLOGY B

Wednesday, 9 00 a m

PINE ROOM—CONGRESS HOTEL

### Analgesic Drugs

- 1 B Calesnick (by invitation) and R Beutner, *Dept of Pharmacology, Hahnemann Medical College, Philadelphia, Penna*

Anti enzymatic action of salicylates and related drugs, tested by new in vitro method

- 2 Paul K Smith and (by invitation) Herbert A Hand and Robert J Madden, *Dept of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
The hydrolysis of acetylsalicylic acid by animal tissues

- 3 E Leong Way, Rollan Swanson and Abraham I Gimble (introduced by Paul K Smith), *Dept of Pharmacology, The George Washington University School of Medicine Washington, D C*

The influence of the liver on the activity of isonipicaine (demerol) in vivo and in vitro

- 4 H B Haag, J K Finnegan (by invitation) and P S Larson, *Dept of Pharmacology, Medical College of Virginia, Richmond*  
Pharmacologic observations on 1,1 diphenyl 1-(dimethyl aminoisopropyl) butanone 2

- 5 Elizabeth B Trovil (introduced by Raymond N Bieter), *Dept of Pharmacology University of Minnesota, Minneapolis*

The analgesic action of 1,1 diphenyl 1 (dimethylaminoisopropyl) butanone 2 in man

- 6 L A Woods (by invitation), J B Wyngaarden (by invitation) and M H Seevers, *Dept of Pharmacology, Univ of Michigan*  
The addiction potentialities of 1,1 diphenyl-1 (dimethylamino isopropyl) - butanone-2 (Amidone) in the monkey

- 7 F E Shideman and H T Johnson (by invitation), *Dept of Pharmacology, University of Michigan*

Acute vascular tolerance to morphine, demerol, and 1,1 diphenyl 1-(dimethylamino isopropyl) butanone 2 (Amidone) in the dog

- 8 Henry W Elliott (introduced by Hamilton H Anderson), *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco*

Comparative effects of 1,1 diphenyl-1-(dimethylaminoisopropyl) butanone - 2 (10320),

demerol, and morphine on the respiration of rat cerebral cortex slices

- 9 Abraham Wikler and Karl Frank (by invitation), *Research Department, U S Public Health Service Hospital, Lexington, Kentucky*

Tolerance and physical dependence in intact and chronic spinal dogs during addiction to 10320 (4-4 - diphenyl - 6 - dimethylamino-heptanone 3)

- 10 C C Scott, K G Kohlstaedt (by invitation), E B Robbins (by invitation), and F W Israel (by invitation), *Eli Lilly and Company, Indianapolis*

Further observations on the pharmacology of dolophine

- 11 Anton C Kirehhof (by invitation) and Norman A David, *Depts of Pharmacology and Anesthesiology, University of Oregon Medical School, Portland, Oregon*

Clinical trial of 6 dimethylamino 4,4-diphenyl 3 heptanone (Dolophine) a synthetic analgesic

- 12 Harris Isbell (by invitation), Anna J Eisenman, Abraham Wikler (by invitation), Mary Daingerfield (by invitation) and Karl Frank (by invitation) *Research Dept, U S Public Health Service Hospital, Lexington, Ky*

Experimental addiction to 10320 (4-4 diphenyl-6 dimethylamino heptanone 3) in man (Biochem)

## PHARMACOLOGY C

Wednesday, 9 00 a m

ENGLISH WALNUT ROOM—CONGRESS HOTEL

- 1 Jacob Sacks, Karl Schoen (by invitation), and S M Gordon (by invitation), *Research Laboratories of Endo Products, Inc, Richmond Hill New York*

Biological properties of a soluble derivative of riboflavin

- 2 B P McNamara (introduced by Stephen Krop), *Pharmacology Section, Medical Division, Edgewood Arsenal, Maryland*

Pharmacological antagonism between stereoisomers of hexachlorocyclohexane

- 3 George P Child (by invitation), R A Woodbury, Richard Torpin (by invitation) W S Boyd (by invitation), J L Allgood (by invitation), J C Neal (by invitation), and H L Cheshire (by invitation), *Depts of Pharmacology and Obstetrics and Gynecology, University of Georgia School of Medicine, Augusta*

Cyclic changes in human uterine pressure curves and the influence of distention and pitressin upon these curves

- 4 Raymond P Ahlquist and R A Woodbury,  
*Dept of Pharmacology, University of Georgia School of Medicine, Augusta, Georgia*  
Influence of drugs, and uterine activity upon uterine blood flow
- 5 R A Woodbury, David Marsh (now with the Univ of West Virginia, Morgantown), Raymond P Ahlquist and Bertha Hobensack (by invitation), *Dept of Pharmacology, Univ of Georgia School of Medicine, Augusta, Georgia*  
The influence of estrogenic substances upon the irritability of the uterine musculature and upon the cardiovascular system
- 6 O S Gibbs, *Gibbs Laboratory, Memphis, Tennessee*  
On the curious pharmacology of hydrastis
- 7 Philip Hitchcock, *Dept of Physiology & Pharmacology, Medical College of Alabama, Birmingham*  
Observations on the pharmacology of aliphatic aldehydes
- 8 G Maresch, Jr, and A Farah (introduced by O Krayser), *Dept of Pharmacology, Harvard Medical School*  
The effect of 2,3-dimercaptopropanol upon the diuretic action of mersalyl
- 9 Leonard Karel and Joseph H Fleisher (introduced by Stephen Krop) *Toxicology Section, Medical Division, Edgewood Arsenal, Md*  
Absorption and diffusion of ethyl alcohol from the stomach of the rat
- 10 V V Cole, S H Hopper (by invitation), and H R Hulpieu, *Depts of Pharmacology and Public Health, Indiana Univ School of Medicine, Indianapolis*  
Some physiological effects of surface active agents
- 11 Shannon C Allen and Floyd DeEds, *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U S Dept of Agriculture, Albany, California*  
Experimental studies on the use of starch as surgical dusting powder
- 12 Frederick F Anderson (by invitation) and Bradford N Craver, *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, New Jersey*  
A compact and efficient apparatus of pyrex glass for coronary perfusion

#### PHARMACOLOGY A

Wednesday, 2 00 p m

UPPER TOWER ROOM—STEVENS HOTEL

#### Histamine, Anti-Histamine and Spasmolytic Drugs

- 1 Paul Achenbach (by invitation) and Earl R Loew, *Dept of Pharmacology, Univ of*

*Illinois College of Medicine, Chicago, 12, Illinois*

Antagonism of histamine with synthetic compounds which exert marked epinephrine-blocking effects

- 2 P K Knoefel, *University of Louisville*  
The evaluation of spasmolytic agents
- 3 Byron B Clark, *Dept of Physiology and Pharmacology, Albany Medical College, Union University, Albany, New York*  
The effect of syntropan, deimerol, and traserline on gastric secretion
- 4 L W Roth, R K Richards and I M Shepperd (introduced by Carl Dragstedt), *Dept of Pharmacology, Abbot Laboratories, North Chicago, Illinois*  
Some pharmacological properties of a new anti-histamine compound
- 5 Julio C Castillo (by invitation) and Edwin J de Beer, *The Wellcome Research Laboratories, Tuckahoe 7, New York*  
The excised guinea-pig trachea in the study of anti-histamine drugs
- 6 A M Schoen (introduced by P K Knoefel), *University of Louisville*  
Comparative "Antihistamine" action on gastric secretion
- 7 Ernest Kun, *Depts of Pharmacology and Medicine, University of Chicago (introduced by E M K Geiling)*  
The effect of meningococcus endotoxin on the distribution of histamine between the blood and tissues of the rabbit
- 8 G Lehmann, Edwina Hagan (by invitation), George Barbarow (by invitation) and Margaret Roe (by invitation), *Research Laboratories, Hoffmann-La Roche, Inc, Nutley, N J*  
The anti-histamine action of pyridindene derivatives
- 9 Floyd C McIntire, L W Roth, and Joseph L Shaw (introduced by H B Haag), *Biochemistry and Pharmacology Departments, Abbott Laboratories, North Chicago, Illinois*  
The purification of histamine for bioassay
- 10 Anne Cameron (by invitation) and Bradford N Craver, *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, New Jersey*  
Contributions to an elucidation of the pharmacological action of histamine
- 11 Charles A Winter, *Merck Institute for Therapeutic Research, Rahway, N J*  
A study of the relative potencies of six anti-histaminic compounds (Physiol)

#### PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Wednesday, 4 30 p m

UPPER TOWER ROOM, STEVENS HOTEL

## PHARMACOLOGY B

Wednesday, 2 00 p m

LOWER TOWER ROOM—STEVENS HOTEL

## Drug Toxicity

- 1 J A Richardson and H R Pratt-Thomas (introduced by R P Walton), *Depts of Pharmacology and Pathology, Medical College of South Carolina, Charleston*

Toxic effects of varying doses of kerosene administered by different routes

- 2 Geoffrey Woodard and Ernest C Hagan (introduced by Arnold J Lehman), *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C*

Toxicological studies on the isomers and mixtures of isomers of benzene hexachloride

- 3 Norman M Keith and Howard B Burchell (by invitation), *Division of Medicine Mayo Clinic, Rochester, Minnesota*

Potassium intoxication in uremia

- 4 R S Teague, *Dept of Physiology and Pharmacology, Medical College of Alabama, Birmingham*

Toxicology of the synthetic estrogen, dienes-trol

- 5 Robert H Wilson, Talbot G Mortarotti (by invitation) and Floyd DeEds, *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U S Dept of Agriculture, Albany, California*

The toxicity and pharmacology of rutin

- 6 G L Cantoni and A W Bernheimer (by invitation), *Dept of Pharmacology, Long Island College of Medicine, Brooklyn, New York and Dept of Bacteriology, New York University College of Medicine, New York, New York*

Specificity of the increased resistance induced in mice by streptococcal toxin

- 7 Stephen Krop, W C Wescoe, 1st Lt, M C (by invitation), Abraham Goldin (by invitation), and Benjamin Landing, 1st Lt, M C (by invitation), *Pharmacology Section and Experimental Pathology Section, Medical Division, Edgewood Arsenal, Maryland*

Central nervous system injury in experimental animals by beta-chloroethyl morpholine

- 8 Harry W Hays, Walter E Barrett, Greta L Holmquist, and Alice A Goodell, (introduced by E Oppenheimer), *Research Division, Department of Pharmacology, Ciba Pharmaceutical Products, Inc, Summit, N J*

The effect of reduced caloric intake on toxicity of N,N dimethyl N'-benzyl N' ( $\alpha$  pyridyl) - ethylenediamine monohydrochloride (Paribenamine)

- 9 P L Ewing and G A Emerson, *Dept of Pharmacology, Univ of Texas Medical Branch, Galveston*

Acute toxicity of benzedrine sulfate

- 10 Jay A Smith (by invitation), Piero P Foa and Harriet R Weinstein (by invitation), *Dept of Physiology, Chicago Medical School*

Some toxic effects of thiamine (Physiol)

## PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Wednesday, 4 30 p m

UPPER TOWER ROOM, STEVENS HOTEL

## PHARMACOLOGY C

Wednesday, 2 00 p m

NORTH ASSEMBLY—STEVENS HOTEL

## Drug Toxicity

- 1 P J Hanzlik, F P Ludueña, W S Lawrence, Jean K Fellows (by invitation) and Others, *Dept of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco 15, California*

Toxicity, excretion and fate of diethylene glycol monoethyl ether compared with other glycols applied epidermally

- 2 A Bass and S C Werch, *Medical Research Division, Plough Inc, Memphis, Tennessee* (Introduced by C C Pfeiffer)

The absorption of phenol in oily solutions by the rabbit skin

- 3 Marie F Whitesell (by invitation), Elsie Alvarez (by invitation) and John H Draize, *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C*

The percutaneous toxicity of thioglycolates

- 4 Irvin Fuhr and Seymour D Silver (introduced by Stephen Krop), *Gassing and Analytical Section, Medical Division, Chemical Corps, Edgewood Arsenal, Md*

The effect of soil on rodenticide vapor concentrations

- 5 Bertram J Meyer, 1st Lt, M C, and Leonard Karel, (introduced by Stephen Krop), *Toxicology Section, Medical Division, Edgewood Arsenal, Maryland*

The effects of thiosorbitol and of iodides on alphanaphthylthiourea toxicity in rats

- 6 Rudolf Koster (introduced by McKee Cattell), *Dept of Pharmacology, Cornell University Medical College*

Differentiation of gluconate, glucose, calcium, and insulin effects on DDT poisoning in cats

- 7 R G Horton, R E Weston, J P Saunders and G Hammon (introduced by Stephen

Krop), *Toxicology Section, Medical Division, Edgewood Arsenal, Maryland*

The conversion of  $-CN$  to  $-CNS$  in dogs

- 8 **Kenneth P DuBois and Emil E Sebesta** (by invitation), *Univ of Chicago Toxicity Laboratory and the Dept of Pharmacology, University of Chicago*

The effect of alpha-naphthylthiourea on peroxidase and catalase

- 9 **O Garth Fitzhugh and Arthur A Nelson** (by invitation), *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C*

The chronic toxicity of chloroquine (SN 7618)

- 10 **Charles M Gruber, Albert M Lupton** (by invitation) and **Thomas M Scotti** (by invitation), *Depts of Pharmacology and Pathology, Jefferson Medical College, Philadelphia, Pa*

Chronic toxicity studies of 1 amino-1-phthalidylpropane hydrochloride and its effects upon blood pressure and respiration

- 11 **Emmett B Carmichael**, *Biochemistry Dept, Medical College of Alabama, Birmingham*  
The toxicity of delvinal sodium for both young and old rats (Physiol)

## PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Wednesday, 4 30 p m

UPPER TOWER ROOM, STEVENS HOTEL

### PHARMACOLOGY A

Thursday, 9 00 a m

PARLORS A, B, AND C—CONGRESS HOTEL

#### Curare and Anti-Curare-Like Drugs

- 1 **C J Kensler** (introduced by McKen Cattell), *Dept of Pharmacology, Cornell University Medical College, New York*

Anti-curare action of certain azo dyes in the frog

- 2 **J H Comroe, Jr, R D Dripps, S Y Botelho** (by invitation) and **H Metz** (by invitation), *Depts of Physiology and Pharmacology, Graduate School of Medicine, and Anesthesiology, University of Pennsylvania School of Medicine*

The curare-like action of ether upon human neuromuscular transmission

- 3 **Lloyd D Seager**, *Dept of Pharmacology, Woman's Medical College of Pennsylvania*  
Some actions of the diamines

#### Anti-Histamine Drugs

- David Fieser**, *Dept of Pharmacology, West Virginia School of Medicine, Morgantown*

Synthetic curare compounds I Biochemorphic aspects of quaternary ammonium iodides derived from cinchona alkaloids

- 5 **M J Reardon** (by invitation), **F A Marzoni** (by invitation) and **James P Hendrix**, *Depts of Surgery and Medicine, Duke University School of Medicine, Durham, N C*

The effect of neostigmine (Prostigmine) on the actions of tetraethylammonium (Etammon) in dogs and man

- 6 **Barbara R Rennick** (by invitation), **Gordon K Moe**, and (by invitation) **Sibley W Hoobler, Rosalie Neligh, and Richard H Lyons**, *Depts of Pharmacology and Internal Medicine, University of Michigan*

Renal excretion of the tetraethylammonium ion

- 7 **Gordon K Moe**, and (by invitation) **Richard H Lyons, Sibley W Hoobler, and Rosalie Neligh**, *Depts of Pharmacology and Internal Medicine, University of Michigan*

The action of tetraethylammonium on receptor mechanisms

- 8 **Mary A Root** (introduced by Otto Kraye), *Dept of Pharmacology, Harvard Medical School*

Effect of tetraethylammonium chloride on the urinary bladder of the cat

- 9 **James L Morrison**, *Dept of Pharmacology, Emory University, Georgia*

The effect of tetraethylammonium bromide on morphine hyperglycemia in dogs

- 10 **D Malton, S W Hoobler, H T Ballantine, Jr, R B Neligh, Saul Cohen and R H Lyons** (introduced by G K Moe), *Depts of Internal Medicine, Surgery and Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan*

The effect of tetraethylammonium on the blood flow in the extremities

## PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Thursday, 12 00 noon

CASINO, CONGRESS HOTEL

### PHARMACOLOGY B

Thursday, 9 00 a m

PINE ROOM—CONGRESS HOTEL

#### Drug Toxicity

- 1 **C H Hine, Lt, M C, USN, T E Shea, Jr, LTCDR, HS, USNR, and W R Alsdorf, CPHM, USN** (introduced by F L Kozella), *National Naval Medical Center, Naval Medical Research Institute, Pharmacology and Toxicology Facility*

An accurate colorimetric method for the determination of methanol in blood, tissues, and the expired air

- 2 T E Shea, Jr, LTCDR, HS, USNR, and C H Hine, Lt, MC, USN (introduced by H A Anderson), *National Naval Medical Center, Naval Medical Research Institute, Industrial Hygiene and Toxicology Facility*

Respiratory excretion of methyl alcohol by white rats

- 3 W S Blakemore, Lt (jg), MC, USNR, and C H Hine, Lt, MC, USN (introduced by P K Smith), *National Naval Medical Center, Naval Medical Research Institute, Pharmacology and Toxicology Facility*

The effect of peritoneal irrigation on methyl alcohol toxicity

- 4 W S Lawrence and L R Capo (by invitation), *Dept of Pharmacology, University of Michigan*

Some limitations of methemoglobinemia in antagonizing cyanide

- 5 Edward H Lanphier (by invitation), Elizabeth H Jenney (by invitation), and Carl C Pfeiffer, *Dept of Pharmacology, University of Illinois College of Medicine*

The use of oximeter to study the potency of p aminophenones as methemoglobin forming drugs

- 6 Alexander G Karezmar (introduced by T Koppanyi), *Dept of Pharmacology and Materia Medica, Georgetown University, School of Medicine*

The effects of lethal doses of acetanilid in the dog

- 7 Elbert Voss (introduced by A L Tatum), *Dept of Pharmacology, Univ of Wisconsin Medical School, Madison*

Effect of PABA as antagonist to organic bismuth preparations

- 8 E H Brunquist, Bertie Warren and Cyrus W Partington (introduced by Richard W Whitehead), *Dept of Physiology and Pharmacology, Univ of Colorado School of Medicine, Denver 7*

Tolerance of excised muscle for sodium sulfadiazine, with prolongation of survival by certain concentrations

- 9 Edwin P Laug (by invitation), Frieda M Kunze (by invitation) and O Garth Fitzhugh, *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C*

Mercury storage in the rat following ingestion of mercuric acetate and phenyl mercuric acetate

- 10 F Garcia-Valdecasas (by invitation) and R Beutner, *Depts of Pharmacology of the University of Barcelona, Spain, and Hahne-*

*mann Medical College, Philadelphia, Pennsylvania*

Explanation of Straub's theory of "Potential Poisons" based on the measurements of electrical potential differences

## PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Thursday, 12 noon

CASINO, CONGRESS HOTEL

## PHARMACOLOGY C

Thursday, 9 00 a m

ENGLISH WALNUT ROOM—CONGRESS HOTEL

### Antibiotic and Chemotherapeutic Agents

- 1 Andres Goth (introduced by Arthur Grollman), *Dept of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas*  
The antibiotic properties of a bismuth "Aspergillus Acid" complex

- 2 Henry M Suckle (by invitation), Roland R Liebenow (by invitation) and O S Orth, *Depts of Neurosurgery, Physiology and Pharmacology, State of Wisconsin General Hospital and Univ of Wisconsin Medical School, Madison*

The convulsive effects of streptomycin

- 3 Harry Eagle and Elliot V Newman (by invitation), *Laboratory of Experimental Therapeutics of the U S Public Health Service and The Johns Hopkins School of Hygiene, and the Dept of Medicine of The Johns Hopkins Medical School*

The renal clearance of penicillins F, G, K, and X, and of bacitracin in rabbits and man

- 4 Karl H Beyer, A Kathrine Miller (by invitation), Horace F Russo (by invitation) and Elizabeth K Tillson (by invitation), *Depts of Pharmacology and Bacteriology, The Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa*

The effect of caronamide on the renal tubular transport mechanisms for penicillin and other agents

- 5 E E Mandel and J D Thayer (introduced by F Steigmann), *U S Marine Hospital, Staten Island, New York*

Rectal administration of penicillin

- 6 M I Smith, Wm T McClosky, E L Jackson (by invitation) and Hugo Bauer (by invitation), *Division of Physiology, National Institute of Health, Bethesda, Maryland*

The chemotherapeutic action of streptomycin and sulfone derivatives in experimental tuberculosis

- 7 L H Schmidt, Carl C Smith (by invitation), Hettie B Hughes (by invitation), and

Catherine Carter (by invitation), Christ Hospital Institute of Medical Research, Cincinnati, Ohio

Studies on the 8-aminoquinolines 1 The toxicities of pamaquine and plasmodin in different animal species

8 Ida G Schmidt (by invitation) and L H Schmidt, College of Medicine, University of Cincinnati, and the Christ Hospital Institute of Medical Research, Cincinnati, Ohio

Studies on the 8-aminoquinolines 2 The effects of plasmodin on the central nervous system

9 Carl C Smith (by invitation) and L H Schmidt, Christ Hospital Institute of Medical Research, Cincinnati, Ohio

Studies on the 8-aminoquinolines 3 On the relations between structure and pharmacological activities

10 Hamilton H Anderson, Eder Lindsay Hansen (by invitation), Peter P T Sah and John R Cafiso (by invitation), Division of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco

Amebaecidal and pharmacologic activities of the dithiocarbonylmethyl and dithiocarbonylphenyl derivatives of carbarsone oxide, (p-carbamidophenylarsenous oxide)

11 R M Featherstone (introduced by E G Gross) and J R Porter (introduced by W M Hale), Depts of Pharmacology and Bacteriology, College of Medicine, State University of Iowa, Iowa City

Some inhibitory effects of alkaloids on bacterial growth and metabolism

12 Leo G Nutini and Sr Eva Marie Lynch (introduced by Fred W Oberst), Dept of Experimental Medicine, Institutum Divi Thomae, Cincinnati

Response of penicillin-resistant strains of staphylococcus aureus to extract of beef brain

cology and Experimental Therapeutics, University of California Medical School, San Francisco, and Department of Physiology and Pharmacology, Baylor University College of Medicine, Houston, Texas

Preliminary observations on the influence of ergotamine and dihydroergotamine on cerebral blood flow in the dog

2 Walter E Barrett (by invitation), Harry W Hays (by invitation), James H Leatham and Alice A Goodell (by invitation), (introduced by Fredrick F Yonkman), Research Division, Department of Pharmacology, Ciba Pharmaceutical Products, Inc, Summit, New Jersey

Toxicity of a new antiseptic ( $\beta$  phenoxy ethyl-dimethyl dodecyl ammonium bromide) (PDDDB)

3 W Dean Belnap (by invitation), James E P Toman and Louis S Goodman, Departments of Physiology and Pharmacology, University of Utah School of Medicine, Salt Lake City, Utah

Tridione-diphenylhydantoin combination therapy in grand mal with slow-wave EEG dysrhythmia

4 Walter M Booker, Hamilton Perkins and Alvin Blount (introduced by A H Maloney), Department of Pharmacology, Howard University School of Medicine

Depression of the thyroid gland by sulfathiazole, the effects on the pancreas

5 Ernest Bueding, Aeme Higashi (by invitation), Lawrence Peters, and Arthur D Valk, Department of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio

Some observations on the action of miracid [1 -  $\beta$  - Diethylamino - ethylamino) - 4 - Methylthioxanthone hydrochloride] against *Schistosoma mansoni*

6 Ernest Bueding, Lawrence Peters, and Arnold D Welch, Dept of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio

Metabolism of Schistosomes (*S. mansoni*)

7 G L Cantoni, Department of Pharmacology, Long Island College of Medicine, Brooklyn, New York

Acid Soluble Phosphorus Compounds of Heart Muscle

8 James Y P Chen (by invitation) and Benedict E Abreu, Division of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco

Effect of carbon tetrachloride poisoning on the toxicity of  $\beta$ -diethylaminoethyl phenyl  $\alpha$ -thioethylacetate and benadryl

## PHARMACOLOGICAL SOCIETY BUSINESS MEETING

Thursday, 12 00 noon  
CASINO, CONGRESS HOTEL

### MOTION PICTURES

Thursday, 1 00-5 00 p m  
Room 14, Palmer House  
(for program see p 3)

### PHARMACOLOGY

Papers Read by Title

Benedict E Abreu, Grant W Liddle (by invitation), Carroll A Handley and Henry W Elliott (by invitation) Division of Phar-

- 9 Yin-ch'ang Chin (*introduced by* Hamilton H Anderson), *Division of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco*  
Biologic properties of subtilin in physiologic saline solution
- 10 Elizabeth M Cranston, Mary Jane Jensen, Adelaide Moren, Theresa Brey, E T Bell and Raymond N Bieter, *Bureau of Plant Industry USDA and the Departments of Pharmacology and Pathology, University of Minnesota, Minneapolis*  
The acute and chronic toxicity of nordihydroguaiaretic acid
- 11 Bradford N Craver, *Ciba Pharmaceutical Products, Inc, 556 Morris Avenue, Summit, New Jersey*  
Effect of X-ray in vitro upon the contractility of the isolated intestine of the cat
- 12 Bradford N Craver, Patricia Seip (*by invitation*) and James Smith (*by invitation*), *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, New Jersey*  
Some pharmacological properties of imidazoline and aryloxyacetamide hydrochlorides
- 13 John E Davis and Alfred H Lawton (*by invitation*), *Dept of Physiology and Pharmacology, University of Arkansas*  
Antagonism of the vasopressor action of nicotine by potassium thiocyanate
- 14 M Edward Davis (*by invitation*) and Nicholas W Fugo, *Depts of Obstetrics and Gynecology and the Dept of Pharmacology, The University of Chicago and The Chicago Lying-in Hospital*  
The effects of toxic doses of thiouracil on the reproductive system of the male rat
- 15 M Edward Davis (*by invitation*), Nicholas W Fugo, and Kenneth G Lawrence (*by invitation*), *Depts of Obstetrics and Gynecology and the Dept of Pharmacology, The University of Chicago and The Chicago Lying in Hospital*  
The effect of alloxan diabetes on reproduction in the female rat
- 16 Wm B Deichmann and S Witherup (*by invitation*), *Kettering Lab of Applied Physiology, College of Medicine, University of Cincinnati, Cincinnati, Ohio*  
The immediate toxicity of hexaethyltetraphosphate, tetraethylpyrophosphate, and hexaoctyltetraphosphate to rabbits and rats
- 17 Harold De Mars, Guy Boyden, Ben Vidgoff, and E Hendricks (*introduced by* N David), *Department of Pharmacology, University of Oregon Medical School*
- Influence of endocrine imbalance on middle ear structure I Histological study in white rat
- 18 Robert H Dreisbach, *Dept of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, California*  
Failure of benadryl and pyribenzamine in experimental skin sensitization to penicillin and horse serum
- 19 N B Dreyer and Cleveland Denton (*by invitation*), *Dept of Pharmacology, University of Vermont*  
Some autonomic nervous system responses to benadryl
- 20 N B Dreyer and Donald Harwood (*by invitation*), *Dept of Pharmacology, University of Vermont*  
 $\beta$  ionone, A sympatholytic agent
- 21 N B Dreyer and Donald Harwood (*by invitation*), *Dept of Pharmacology, University of Vermont*  
A method for testing anti spasmodics on the cat's intestine in situ
- 22 Victor A Drill and Carroll A Pfeiffer, *Depts of Pharmacology and Anatomy of Yale University School of Medicine, New Haven, Connecticut*  
Estrogenic changes in normal rats fed a low protein diet
- 23 Robert L Driver (*introduced by* P J Hanzlik), *Dept of Pharmacology and Therapeutics, Stanford University School of Medicine, San Francisco, California*  
Further studies of anticonvulsant actions of compounds chemically related to isopropyl alcohol
- 24 Robert L Driver and G L Ordway (*introduced by* P J Hanzlik) *Dept of Pharmacology and Therapeutics, Stanford Univ School of Medicine, San Francisco, California*  
Comparative anticonvulsant actions of isopropyl alcohol, diphenylhydantoin, phenobarbital and tridione
- 25 Kenneth P DuBois, Wilma F Erway (*by invitation*), and Richard U Byerrum (*by invitation*), *University of Chicago Toxicity Laboratory and the Department of Pharmacology, University of Chicago*  
A comparison of cholinesterase inhibitors in vitro and in vivo
- 26 P L Ewing and G A Emerson, *Dept of Pharmacology, Univ of Texas Medical Branch, Galveston*  
Influence of optical isomers of amphetamine on maze performance in rats
- 27 Nicholas W Fugo and Gloria T Aragon (*by invitation*), *Dept of Obstetrics and Gynecology and the Dept of Pharmacology, The*



*University of Chicago and the Chicago Lying-in Hospital*

The utilization of an old technique for a sensitive antidiuretic assay

- 28 N J Giacomino (by invitation) and E L McCawley, *Dept of Pharmacology and Toxicology, Yale University, School of Medicine, New Haven, Connecticut*

On the toxic reactions of unsaturated lactones and their saturated analogs

- 29 Donald R Hales and Arnold D Welch, *Dept of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio*

Experimental study of the anthelmintic value of the cyanine drugs in dogs

- 30 Lawrence W Hanlon (by invitation), Harry Gold, Walter Modell, Joseph G Benton (by invitation), and Elaine W Cotlove (by invitation), *Dept of Pharmacology of Cornell Univ Medical College, and Cardiac Services of Beth Israel Hospital and Hospital for Joint Diseases, New York*

Absorption of Digoxin in man

- 31 Harry W Hays (by invitation), Walter E Barrett (by invitation), Elizabeth A Herrold (by invitation), Barbara R Richards (by invitation), Anne Mackenzie (by invitation) and Fredrick F Yonkman, *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc, Summit, New Jersey*

Some pharmacologic effects of an antiseptic,  $\beta$  phenoxy-ethyl-dimethyl dodecyl ammonium bromide (PDDDB)

- 32 Hettie B Hughes (by invitation) and L H Schmidt, *Christ Hospital Institute of Medical Research, Cincinnati, Ohio*

On the metabolism of paludrine in the rat

- 33 Harris Isbell (by invitation), Anna J Eisenman (by invitation), Abraham Wikler, Mary Daingerfield (by invitation), and Karl Frank (by invitation), *Research Department, U S Public Health Service Hospital, Lexington, Kentucky*

Treatment of the morphine abstinence syndrome with 10820 (4-4 diphenyl-6 dimethylamino-heptanone-3)

- 34 Harris Isbell (by invitation), Abraham Wikler, Anna J Eisenman (by invitation), and Karl Frank (by invitation), *Research Department, U S Public Health Service Hospital, Lexington, Kentucky*

Effect of single doses of 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3) on man

- 35 Leonard Karel, Benjamin H Landing, and Thomas S Harvey (introduced by Stephen Krop), *Toxicology and Pathology Sections, Medical Division, Edgewood Arsenal, Maryland*

The intraperitoneal toxicity of some glycols, glycol ethers, glycol esters, and phthalates in mice

- 36 Leonard Karel and Raymond E Weston (introduced by Stephen Krop) *Toxicology Section, Medical Division, Edgewood Arsenal, Maryland*

Femoral arterial and venous blood nitrogen content of dogs during denitrogenation by continuous oxygen inhalation

- 37 Norman W Karr (introduced by N A David), *Dept of Pharmacology, University of Oregon Medical School, Portland, Oregon*

Effects of 6-dimethylamino-4,4-diphenyl-3-heptanone (Dolophine) on intestinal motility

- 38 Norman W Karr and I H Perry (introduced by N David), *Depts of Pharmacology and Pathology, University of California Medical School, San Francisco and Dept of Pharmacology, Univ of Oregon Medical School, Portland, Oregon*

Chronic toxicity of certain anti-cholinesterase drugs

- 39 Anton C Kirchhof and John K Uchiyama (introduced by N David), *Depts of Pharmacology and Anesthesiology, University of Oregon Medical School, Portland, Oregon*

Prothrombin time following curarization

- 40 Anton C Kirchhof and John K Uchiyama (introduced by N David) *Department of Pharmacology, University of Oregon Medical School, Portland, Oregon*

Spasmolytic action of 6-dimethylamino-4,4-diphenyl-3-heptanone (Dolophine), a synthetic analgesic

- 41 Stephen Krop, *Pharmacology Section, Medical Division, Edgewood Arsenal, Maryland*

The effect of di-isopropylfluorophosphate, diisopropylchlorophosphate, diisopropyl phosphite and diisopropylphosphate on the mechanical response of striate frog muscle

- 42 W S Lawrence, *Dept of Pharmacology, University of Michigan*

The toxicity of sodium cyanide at slow rates of infusion

- 43 R C Li, *Dept of Pharmacology, Peking Union Medical College, Peking, China*

Gonadotrophic potency of the pituitary of rats after desoxycorticosterone

- 44 Roland R Liebenow (by invitation) and O Sidney Orth, *Dept of Pharmacology, Univ of Wisconsin Medical School, Madison, Wisconsin*

Further studies of the effects of chloroform on cardiac irregularities in the dog

- 45 Earl R Loew and Audrey Micetich (by invitation), *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12, Illinois*

- A method for selection of synthetic compounds which prevent excitatory responses to epinephrine
- 46 S Loewe and Roger Adams (*by invitation*), *Dept of Pharmacology, University of Utah School of Medicine, Salt Lake City, Utah, and Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois*  
Structure activity relationship (SAR) and pharmacological peculiarities of new synthetic congeners of tetrahydrocannabinol
- 47 S Loewe and Louis S Goodman, *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City, Utah*  
Anticonvulsant action of marihuana active substances
- 48 E L McCawley and J Belford (*by invitation*), *Dept of Pharmacology and Toxicology, Yale University School of Medicine, New Haven, Conn*  
On the toxicity of curare in animals maintained with artificial respiration
- 49 W A McOmie (*introduced by Hamilton H Anderson*), *Division of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco, California*  
Local and systemic effects of 2 methyl 2,4 pentanediol (hexylene glycol)
- 50 W A McOmie (*by invitation*), R W Pickering (*by invitation*, and Hamilton H Anderson, *Division of Pharmacology and Experimental Therapeutics, University of California Medical School, San Francisco*  
Analeptic properties of 2,4 dimethyl sulfolane
- 51 Mark Nickerson (*by invitation*) and Louis S Goodman, *Dept of Pharmacology, University of Utah School of Medicine, Salt Lake City, Utah*  
Synergistic isonipecaïne-amphetamine analgesia
- 52 Mark Nickerson, James E P Toman, and H H Hecht (*introduced by Louis S Goodman*), *Depts of Pharmacology, Physiology and Medicine, University of Utah School of Medicine, Salt Lake City, Utah*  
Effect of atropine on epinephrine induced cardiac irregularities
- 53 O Sidney Orth, Robert A Capps (*by invitation*), and Henry M Suckle (*by invitation*), *Dept of Pharmacology, University of Wisconsin Medical School, Madison*  
Some pharmacological properties of dihydroergocornine (DHO 180)
- 54 Lawrence Peters, William B Wartman, Allen Moore (*by invitation*), Aeme Higashi (*by invitation*), and Ernest Bueding, *Dept of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio, and Dept of Pathology, School of Medicine, Northwestern University, Chicago, Illinois*  
The chronic toxicity of 1-ethyl 3,6-dimethyl-2-phenyl-4-pyrimido-2-cyanine chloride (CMR #863) for dogs and monkeys
- 55 Calvin Plumbhof, J Victor Stevenson, and James E P Toman (*introduced by Louis S Goodman*), *Depts of Pharmacology and Physiology, University of Utah School of Medicine, Salt Lake City, Utah*  
Antidiuretic response in dogs following intracarotid injection of hypertonic sodium chloride solution
- 56 H J Pratt (*by invitation*) and R Beutner, *Dept of Pharmacology, Hahnemann Medical College*  
Comparative measurements of the antihistamine effects
- 57 R K Richards, L W Roth, and K Kueter (*introduced by Carl Dragstedt*), *Dept of Pharmacology, Abbott Laboratories, North Chicago, Illinois*  
Pharmacologic action of some quarternary ammonium derivatives of procaine
- 58 Eugene D Robin (*by invitation*), Celia White Tabor (*by invitation*), and Paul K Smith, *Dept of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
Studies on the toxicity of para-aminobenzoic acid in rats
- 59 William T Salter, Wallace F White (*by invitation*), and Elizabeth M Ackerman (*by invitation*), *Laboratory of Pharmacology and Toxicology, Yale University School of Medicine, New Haven, Conn*  
A quantitative theory how digitoxin congeners act on hypodynamic myocardium
- 60 L H Schmidt, Hettie B Hughes (*by invitation*), and Carl C Smith (*by invitation*), *Christ Hospital Institute of Medical Research, Cincinnati, Ohio*  
On the pharmacology of paludrine
- 61 R Shore (*introduced by P K Knocfel*), *University of Louisville*  
Urinary excretion of cetyl pyridinium
- 62 Henry M Suckle (*by invitation*), Roland R Liebenow (*by invitation*), and O Sidney Orth, *Depts of Physiology, Neurosurgery and Pharmacology, Univ of Wisconsin Medical School and State of Wisconsin General Hospital, Madison*  
Effects of diethyl ether, chloroform and cyclopropane on spontaneous cardiac irregularities in the macacus rhesus
- 63 Rolan Swanson (*by invitation*), Joseph Ney (*by invitation*), and Paul K Smith, *Dept of Pharmacology, The George Washington Uni-*

- versity School of Medicine, Washington, D C*  
Influence of BAL on the acute toxicity of gold salts in mice
- 64 Celia White Tabor (*by invitation*), Judith Bailly (*by invitation*), and Paul K Smith, *Dept of Pharmacology, George Washington University School of Medicine, Washington, D C*  
The metabolism of para-aminobenzoic acid in patients with diminished liver function
- 65 Charles H Taft (*introduced by G A Emerson*), *Pharmacology Dept, Medical Branch, The University of Texas, Galveston and The Marine Biological Laboratory, Woods Hole, Mass*  
The action of various cinchona alkaloids on the isolated heart of *limulus polyphemus*
- 66 Charles H Taft (*introduced by G A Emerson*), *Pharmacology Dept, Medical Branch, The University of Texas, Galveston*  
Comparative hyperglycemic responses of rabbits to injections of levo and racemic epinephrine
- 67 Charles H Taft and Helen B Taft (*introduced by G A Emerson*), *Pharmacology Department, Medical Branch, The University of Texas, Galveston*  
Speed of hyperglycemic response in rabbits to intravenous injection of epinephrine
- 68 Karl F Urbach, William C North, and Joseph L Glaser (*introduced by Carl A Dragstedt*), *Dept of Pharmacology, Northwestern University Medical School, Chicago, Illinois*  
A preliminary report on the local anesthetic properties of various aromatic carboxylic acid esters
- 69 R P Walton, M Belkin (*by invitation*), and O J Brodie (*by invitation*), *Dept of Pharmacology, Medical College of South Carolina*  
Pharmacologic characterization of an aliphatic amine, 2-methyl-amino 6-hydroxy-6-methyl heptane
- 70 E Leong Way, Samuel S Binder, and Arnold H Michael (*introduced by Paul K Smith*), *Dept of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
One way isonipicaine-trimethadione antagonism
- 71 E Leong Way, Abraham I Gimble, and E William Ligon, Jr (*introduced by Paul K Smith*), *Dept of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
The tissue distribution of isonipicaine (demerol)
- 72 E Leong Way, Robert C Grubbs, and Rollan Swanson (*introduced by Paul K Smith*), *Dept of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
The effects of isonipicaine (demerol) on auricular fibrillation
- 73 E Leong Way, John R Overman, and Donald L Howie (*introduced by Paul K Smith*), *Dept of Pharmacology, The George Washington University School of Medicine, Washington, D C*  
Studies on the urinary excretion of  $\beta$ -dimethyl aminoethylbenzhydryl ether hydrochloride (benadryl)
- 74 Abraham Wikler, Karl Frank (*by invitation*), and Anna J Eisenman (*by invitation*), *Research Department, U S Public Health Service Hospital, Lexington, Kentucky*  
Effects of single doses of 10820 (4,4-diphenyl 6-dimethylaminoheptanone-3) on the nervous system of dogs and cats
- 75 W Lane Williams, Fred G Brazda, and Margaret S Wiedorn (*introduced by R N Bieter*), *Depts of Anatomy and Biochemistry, Louisiana State University School of Medicine and the Dept of Anatomy, University of Minnesota*  
Effects of naphuride sodium (Suramin) on respiration and morphology of lymphoid tissues of rats
- 76 W M Wilson (*by invitation*), A C Kirchhof (*by invitation*), and N David, *Department of Pharmacology, University of Oregon Medical School, Portland, Oregon*  
Further studies on d-lysergic acid, d- $\alpha$  hydroxybutylamide 2 (Methergine)
- 77 L A Woods (*by invitation*), J B Wyngaarden (*by invitation*), Barbara Rennick (*by invitation*), and M H Seevers, *Dept of Pharmacology, Univ of Michigan*  
The cardiovascular effects of sodium pentothal and sodium 5-allyl-5-(1-methylbutyl)-2 thio barbiturate in the dog
- 78 J B Wyngaarden (*by invitation*), L A Woods (*by invitation*), and M H Seevers, *Dept of Pharmacology, Univ of Michigan*  
The cumulative action of certain thiobarbiturates in dogs
- 79 Carl C Pfeiffer, Elizabeth H Jenney (*by invitation*), and Charles H Ross (*by invitation*), *Department of Pharmacology, University of Illinois College of Medicine, Chicago*  
Time relationships in the reversal by BAL of the chemotherapeutic effect of mapharsen
- 80 P C Eisman, M Rodbart, F C Kull, and R L Meyer (*introduced by Frederick F Yonkman*), *Research Division, Ciba Pharmaceutical Products, Inc, Summit, N J*  
Bacteriostatic and bactericidal properties of  $\beta$ -phenoxy ethyl-dimethyl-dodecyl ammonium bromide (PDDB) and as a skin and instrument disinfectant

## THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

## THIRTY-SECOND ANNUAL MEETING

## PATHOLOGY

Monday, 9 00 a m (promptly)

PALMER HOUSE, ROOM 14

Joint Meeting with the American Association  
of Immunologists

(For program see Immunology p 65)

## JOINT SESSION OF THE FEDERATION

Monday, 1 45 p m

GRAND BALLROOM, STEVENS HOTEL

Program on p 3

## PATHOLOGY

Tuesday, 9 00 a m

PALMER HOUSE, ROOM 14

## Neoplasms, Radiation, Isotopes

- 1 Anderson Nettleship, *Department of Pathology, Alexander Blain Hospital, Detroit*

Tissue elements in the origin of neoplasms  
Morphologic evidence that certain neoplasms  
have multicellular origin

- 2 Thelma B Dunn and Margaret K Deringer  
(*by invitation*), *National Cancer Institute, Bethesda*

Observations on normal and neoplastic mast  
cells in inbred strains and hybrid mice

- 3 Peter A Herbut (*introduced by* Hobart A Reimann), *Department of Pathology, Jefferson Medical College, Philadelphia*

Cancer cells in prostatic secretions

- 4 Paul E Steiner, D Warren Stanger (*by invitation*), and Miriam N Bolyard (*by invitation*), *Department of Pathology, The University of Chicago*

Carcinogenic substances in extracts of human  
lungs

- 5 Ivor Cornman and Richard A Ormsbee (*introduced by* Cornelius P Rhoads), *The Sloan-Kettering Institute for Cancer Research, New York*

The different susceptibilities to nitrogen  
mustard of normal and malignant tissues  
growing *in vitro*

- 6 Paul Goldhaber, Ivor Cornman, and Richard A Ormsbee (*introduced by* Cornelius P Rhoads), *The Sloan-Kettering Institute for Cancer Research, New York*

Experimental alteration of the ability of tumor  
cells to lyse plasma clots *in vitro*

- 7 Bradford N Craver, *Ciba Pharmaceutical Products, Inc, Summit*

The role of adrenal cortical injury in the toxic  
effects of X-ray exposure (*Pharm*)

- 8 Egon Lorenz and Allen B Eschenbrenner, *National Cancer Institute and National Argonne Lab, Chicago*

The role of intensity of chronic irradiation  
with gamma and x-rays

- 9 Allen B Eschenbrenner, Egon Lorenz, Eliza Miller (*by invitation*), *National Cancer Institute and National Argonne Laboratory, Chicago*

Quantitative histologic study of the effect of  
chronic whole-body gamma irradiation on  
mouse testes

- 10 P F Hahn, Ella Lea Carothers (*by invitation*), R O Cannon (*by invitation*), C W Sheppard (*by invitation*), W J Darby, M M (*by invitation*), *Departments of Biochemistry, Medicine, Obstetrics, and Preventive Medicine, Vanderbilt University Medical School, Nashville*

Iron uptake in 750 cases of human pregnancy  
using the radioactive isotope  $Fe^{59}$

- 11 Charles L Yuile, Chauncey G Bly (*by invitation*), and John C Wells (*by invitation*), *Department of Pathology, University of Rochester School of Medicine and Dentistry*

Plasma and red cell radioiron following intra-  
venous injection Sterile abscesses in normal  
and anemic dogs

- 12 C W Sheppard (*by invitation*) and P F Hahn, *Department of Biochemistry, Vanderbilt University, Nashville*

The use of colloidal radioactive gold in medical  
therapy

## PATHOLOGY

Tuesday, 2 00 p m

PALMER HOUSE, ROOM 14

Plasma Proteins, Amino Acids, Phospholipids,  
Vitamins, Hormones

- 1 P R Cannon, C H Steffee (*by invitation*), L J Frazier (*by invitation*), D A Rowley (*by invitation*), and R C Stepto (*by invitation*), *Department of Pathology, The University of Chicago*

The influence of time of ingestion of essential  
amino acids upon utilization in tissue syn-  
thesis

- 2 **Ralph E Knutti**, *University of Rochester and Childrens Hospital of Los Angeles*  
Effects of various protein diets on colloids (plasma protein and gum acacia) in the blood
- 3 **Frank W McKee**, **Paul R Schloerb**, and **Garson H Tishkoff** (introduced by **George H Whipple**), *Department of Pathology, University of Rochester School of Medicine and Dentistry*  
Protein metabolism studies in dogs with partial constriction of inferior vena cava
- 4 **C E Dent** (introduced by **F S Robscheit-Robbins**), *Medical Unit, University College Hospital, London, and Department of Pathology, University of Rochester*  
Mechanisms of aminoaciduria
- 5 **Jesse L Bollman**, **Eunice V Flock**, **John H Grindlay**, and **James C Cain** (by invitation), *The Mayo Foundation, Rochester, Minnesota*  
Phospholipids in thoracic duct lymph of rats
- 6 **James F Rinehart** and **Louis D Greenberg** (by invitation), *Departments of Pathology and Pharmacology, University of California Medical School, San Francisco*  
Folic acid deficiency in the monkey
- 7 **Charles W Mushett** (introduced by **W B Castle**), *Merck Institute for Therapeutic Research, Rahway*  
Pathologic alterations resulting from the administration of 2,4-dimethyl-3-hydroxy-5-hydroxymethyl-pyridine, an analogue of pyridoxine
- 8 **Charlotte L Maddock** (by invitation), **S Burt Wolbach**, **Stephen Maddock**, and **Dorothy Jensen** (by invitation), *Department of Pathology, Harvard Medical School and The Surgical Research Laboratory, Boston City Hospital*  
Hypervitaminosis A in the dog
- 9 **Albert Segaloff**, *The Alton Ochsner Medical Foundation, New Orleans*  
The metabolism of some estrogen degradation products
- The preparation of prothrombin by adsorption on, and elution from aluminum hydroxide
- 2 **Anthony J Glazko**, *Department of Biochemistry, Emory University, Ga*  
Stability of thrombin in the presence of fibrinolysin
- 3 **Leandro M Tocantins** and **John N Lindquist** (by invitation), *Jefferson Medical College, Philadelphia*  
Thromboplastin in the urine of normal and hemophilic men
- 4 **Peter R Morrison** (introduced by **John T Edsall**), *Department of Physical Chemistry, Harvard Medical School*  
On the determination of fibrinogen (*Biochem*)
- 5 **John D Ferry**, **John T Edsall**, **Peter R Morrison** (by invitation), **Victor Kimel** (by invitation), and **Walter F Lever** (by invitation), *Department of Physical Chemistry, Harvard Medical School*  
Some factors influencing the structure and rate of formation of fibrin clots
- 6 **Joseph Lein** (introduced by **Robert Gaunt**), *Department of Zoology, Syracuse University and the Department of Biology, Princeton University*  
A photometric analysis of fibrin formation
- 7 **Alfred Lewin Copley**, *Marine Biological Laboratory, Woods Hole, Mass, and Laboratory of Cellular Physiology, Department of Biology, New York University*  
The clotting of limulus blood
- 8 **L B Jaques**, **M Rocha e Silva** (by invitation), **A Evelyn Scroggie** (by invitation), *Department of Physiology, University of Saskatchewan, Saskatoon*  
Fibrinolysis in peptone shock
- 9 **M Mason Guest**, **Byrne M Daly** (by invitation), **Arnold G Ware** (by invitation), and **Walter H Seegers**, *Department of Physiology, Wayne University College of Medicine, Detroit*  
Quantitative measurements of a fibrinolysin inhibitor in the plasma of various species
- 10 **J H Ferguson**, **B L Travis** (by invitation), and **E B Gerheim** (by invitation), *Department of Physiology, University of North Carolina, Chapel Hill*  
Trypsin (plasmin) and blood coagulation
- 11 **Betty Wilson** (by invitation) and **A J Glazko**, *Department of Biochemistry, Emory University Medical School, Emory University, Ga*  
Determination of serum antiprotease
- 12 **K M Brinkhous**, *Departments of Pathology, State University of Iowa and University of North Carolina*  
Clotting defect in hemophilia Deficiency in a

## PATHOLOGY

Wednesday, 9 00 a m

PALMER HOUSE, ROOM 14

Joint Meeting with the American  
Physiological Society

## Coagulation

- 1 **F L Munro** and **Muriel Platt Munro** (introduced by **J E Thomas**), *Charlotte Drake Cardeza Foundation, Department of Medicine, Jefferson Medical College and Hospital, Philadelphia*

plasma factor required for thromboplastin liberation from platelets

- 13 J Garrett Allen, *Department of Surgery, University of Chicago*

Hyperheparinemia The cause of the hemorrhagic disease produced by total body exposure to ionizing irradiation

### PATHOLOGY

Wednesday, 2 00 p m

PALMER HOUSE, ROOM 14

Business Meeting, 4 30 p m

### Hematology

- 1 Bernhard Steinberg and Virginia Hufford (by invitation), *Toledo Hospital Institute of Medical Research*

Development of complete marrow in adult animals

- 2 John W Rebuck and Helen L Woods (introduced by F W Hartman), *Department of Laboratories, Henry Ford Hospital, Detroit*  
Electron microscope studies of blood cells in the hematopoietic organs and inflammatory exudates of man

- 3 Raphael Isaacs, *Michael Reese Hospital, Laboratory of Hematology*

Conversion of acute into chronic leukemia

- 4 Louis Levin, *Department of Hematology, Michael Reese Hospital*

Studies on adrenocortical function in relation to lymphatic leukemia (*Biochem*)

- 5 Joseph L Lalech, *Department of Pathology, University of Wisconsin Medical School, Madison*

The influence of injections of homologous hemoglobins into normal and dehydrated animals

- 6 George S Samuelson (by invitation), Grace E Griffin (by invitation), Edward Muntwyler, and Sam Seifter, *Department of Biochemistry, Long Island College of Medicine, Brooklyn*

The absorption of blood from the peritoneal cavity of the dog (*Biochem*)

- 7 Vivian G Behrmann (by invitation) and Frank W Hartman, *Department of Laboratories, Henry Ford Hospital, Detroit*

Continuous blood O saturation under pentothal—N O — O anesthesia in clinical and experimental subjects

- 8 Howard C Hopps and Wiley T McCollum (introduced by Paul R Cannon), *Department of Pathology, The School of Medicine of The University of Oklahoma*

Further studies on experimental periarteritis nodosa With special reference to variations

in blood pressure and electrocardiographic changes

- 9 Russell L Holman, *Department of Pathology and Bacteriology, L S U School of Medicine, New Orleans*

Further observations on the possible role of cholesterol in arterial disease

- 10 Charles D Stevens, Henry W Ryder, and Eugene B Ferris (introduced by M A Blankenhorn), *Department of Internal Medicine, College of Medicine, University of Cincinnati*

The rate of nitrogen elimination through the lungs in relation to susceptibility to decompression sickness

### PATHOLOGY

Thursday, 9 00 a m

PALMER HOUSE, ROOM 14

### Injury and Repair

- 1 Murray Franklin (by invitation), Melvin R Salk (by invitation), Hans Popper, and Frederick Steigmann (by invitation), *Cook County Hospital and Hektoen Institute for Medical Research*

Functional significance of the response of fatty metamorphosis of human liver to lipotropic therapy

- 2 Virgil H Moon, *Department of Pathology, Jefferson Medical College*

Renal pathology incident to shock

- 3 Benjamin Highman (introduced by R D Lillie), *National Institute of Health*

Pathological changes produced by inhalation exposures to mono chloro-mono bromo methane

- 4 Arthur A Nelson and O Garth Fitzhugh (by invitation), *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C*

Pathological changes produced by feeding of chloroquine (SN 7618) to rats

- 5 George M Hass and C B Taylor (by invitation), *Department of Pathology, Presbyterian Hospital, Chicago*

A quantitative hypothermic method for production of local injury to tissue

- 6 John W Harman (introduced by D Murray Angevine), *Department of Pathology, University of Wisconsin Medical School, Madison*

Local vascular phenomena induced in skeletal muscle by acute ischemia

- 7 Rolf Lium (by invitation), Stephen Maddock, and Dorothy Jensen (by invitation), *Surgical Research Laboratory, Boston City Hospital*

The experimental production of acute pancreatitis

8. Wilhelm Buschke (*introduced by Selig Hecht*), Wilmer Ophthalmological Institute, Johns Hopkins University

Further observations on epithelial movements in woundhealing (*Physiol*)

9. William E Ehrich and Joseph Seifter (*by invitation*), Philadelphia General Hospital

and The Wyeth Institute of Applied Biochemistry, Philadelphia

The role of the salivary glands in the alarm reaction of Selye

- 10 Isidore Gersh (*introduced by Granville A Bennett*), Department of Pathology, University of Illinois College of Medicine

Polysaccharide complex in individual follicles of the thyroid gland of the rat

## THE AMERICAN INSTITUTE OF NUTRITION

### ELEVENTH ANNUAL MEETING

#### NUTRITION

Monday, 9 00 a m

CASINO, CONGRESS HOTEL

#### General

- 1 William J Darby, Edgar Jones (*by invitation*) Henry F Warden (*by invitation*), and Margaret M Kaser (*by invitation*), Departments of Medicine and of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee

The vitamin M group and gastrointestinal absorption in the human

- 2 D W Woolley, The Rockefeller Institute for Medical Research

Streptogenin activity of peptides of glutamic acid

- 3 Robert R Sealock, Ruth L Goodland (*by invitation*), and Philip L White (*by invitation*), Department of Chemistry, Iowa State College, Ames

Tyrosine oxidation by normal and scorbutic liver extracts

- 4 B Connor Johnson (*by invitation*), H H Mitchell, T S Hamilton, and W B Nevens (*by invitation*), Division of Animal Nutrition and Department of Dairy Husbandry, University of Illinois, Urbana

Vitamin deficiencies in the calf

- 5 H J Almquist, Research Laboratories, F E Booth Co, Inc, Emeryville, California

Evaluation of the amino acid requirements of the chick

- 6 C F Huffman and C W Duncan (*by invitation*), Michigan State College

Unknown dietary factor or factors needed by lactating cows depleted on legume hay alone

- 7 Wanda Willman (*by invitation*), Miriam Brush (*by invitation*), Helen Clark (*by invitation*), and Pearl Swanson, The Nutrition Laboratory, The Foods and Nutrition Section, Iowa

Agricultural Experiment Station, Iowa State College, Ames

Dietary fat and the nitrogen metabolism of rats fed protein-free rations

#### JOINT SESSION OF THE FEDERATION

Monday, 1 45 p m

GRAND BALLROOM, STEVENS HOTEL

Program on p 3

#### AMERICAN INSTITUTE OF NUTRITION DINNER, PRESENTATION OF AWARDS, BUSINESS MEETING

Monday, 6 30 p m

HOTEL CONTINENTAL

#### NUTRITION

Tuesday, 9 00 a m

CASINO, CONGRESS HOTEL

#### Vitamins

- 1 S A Singal (*by invitation*), V P Sydenstricker, and Julia Littlejohn (*by invitation*), Departments of Biochemistry and Medicine, University of Georgia, School of Medicine, Augusta

The role of tryptophane in the nutrition of dogs on nicotinic acid deficient diets

- 2 Herbert P Sarett and Grace A Goldsmith (*by invitation*), Nutrition Research Laboratory, Tulane University School of Medicine, New Orleans, Louisiana

Further observations on the relationship of tryptophane and nicotinic acid metabolism in humans (*Biochem*)

- 3 W D Salmon, Laboratory of Animal Nutrition, Alabama Polytechnic Institute, Auburn

The tryptophane-sparing action of nicotinic acid (*Biochem*)

- 4 A C Groschke, J O Anderson, and G M Briggs (introduced by N R Ellis), *Department of Poultry Husbandry, University of Maryland, College Park*  
Growth inhibitory action of amino acids in nicotinic acid-low diets for chicks (*Biochem*)
- 5 W A Krehl (by invitation), Alberto Carvalho (by invitation), and George R Cowgill, *Yale Nutrition Laboratory, Department of Physiological Chemistry, Yale University*  
Strain differences in the niacin requirement of the rat
- 6 James M Hundley (introduced by F S Daft), *Division of Physiology, National Institute of Health, Bethesda, Maryland*  
Production of niacin deficiency in rats
- 7 G J Everson, E K Wheeler, and H J Walker (introduced by Pearl Swanson), *Iowa State College*  
Availability of riboflavin from food sources as judged by urinary excretion of the vitamin
- 8 Agnes Fay Morgan, Mary Groody (by invitation), and Helen E Axelrod (by invitation), *Laboratory of Home Economics, University of California, Berkeley, California*  
Riboflavin deficiency in dogs as affected by the basal diet and by desoxycorticosterone
- 9 P B Pearson, D W Hood (by invitation), and B S Schweigert (by invitation), *Nutrition Laboratory, Agricultural Experiment Station and School of Agriculture, A and M College of Texas, College Station*  
The effect of feeding riboflavin on the fluorometric and microbiological values of milk and urine
- 10 Paul F Fenton (by invitation), and George R Cowgill, *Yale Nutrition Laboratory, Department of Physiological Chemistry, Yale University*  
Studies on the vitamin requirements of highly inbred strains of mice: riboflavin and pantothenic acid
- 11 A E Schaefer (by invitation), C K Whitehair (by invitation), and C A Elvehjem, *Department of Biochemistry, University of Wisconsin, Madison*  
Undenitrified factors essential for growth and hemoglobin production in foxes
- Division, American Cyanamid Company, Pearl River, New York*  
Observations on the pteroylglutamic acid content of the tissues of chickens
- 2 W R Ruegamer (by invitation), Nancy Torbet (by invitation), and C A Elvehjem, *Department of Biochemistry, University of Wisconsin, Madison*  
Hematological and growth responses in dogs given liver extracts containing the anti-pernicious anemia factor (*Biochem*)
- 3 Gertrude Rodney, Marian E Swendseid, and Ann L Swanson (introduced by R A Brown), *Research Laboratories, Parke, Davis and Company*  
Tyrosine oxidation by livers from rats with sulfa induced pteroylglutamic acid deficiency
- 4 Ruth C Steinkamp (by invitation), Carroll F Shukers (by invitation), John R Totter, and Paul L Day, *Department of Biochemistry, School of Medicine, University of Arkansas, Little Rock*  
The excretion of porphyrin by pernicious anemia patients treated with pteroylglutamic acid (*Biochem*)
- 5 A B McCoord (by invitation), B L Goff (by invitation), C F Lavender (by invitation), and S W Clausen, *The Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York*  
The effect of folic acid on the vitamin A stores of rats (*Biochem*)
- 6 W A Krehl (by invitation), Alberto Carvalho (by invitation), and George R Cowgill, *Yale Nutrition Laboratory, Department of Physiological Chemistry, Yale University*  
Pantothenic acid deficiency as affected by diet composition
- 7 Floyd S Daft, *National Institute of Health, Bethesda, Maryland*  
Synthesis of B vitamins by the rat
- 8 W W Cravens and J R Couch (introduced by C A Elvehjem), *Departments of Poultry Husbandry and Biochemistry, University of Wisconsin, Madison*  
Relation of carbohydrate to intestinal synthesis of biotin and hatchability in mature fowl
- 9 Helen T Parsons, Marcella G Polisar (by invitation), and Dolores M Otto (by invitation), *Department of Home Economics, University of Wisconsin, Madison*  
Observations on the nature of the interference of live yeast with availability of thiamine
- 10 Ruth Okey, Richard Pencharz (by invitation), and Samuel Lepkovsky, *Department of Home Economics and the Division of Poultry Research, College of Agriculture, University of California, Berkeley, and the Department of Pathology, Mt Zion Hospital, San Francisco*

## NUTRITION

Tuesday, 2 00 p m

CASINO, CONGRESS HOTEL

## Vitamins

- 1 A L Franklin (by invitation), E L R Stokstad, and T H Jukes, *Lederle Laboratories*



Sex differences in biotin deficient rats fed dried whole egg

- 11 **Max Rubin and H R Bird** (introduced by N R Ellis), *Agricultural Research Center, Beltsville, Maryland*

The chick growth factor of cow manure, a counteractant of effects of excessive soybean meal

## NUTRITION

Wednesday, 9 00 a m

CASINO, CONGRESS HOTEL

### Vitamins

- 1 **Katherine Johnstone Elliott** (by invitation) and **Cecilia Schuck**, *Nutrition Laboratory, School of Home Economics, Purdue University, Lafayette, Indiana*

Utilization by human subjects of crystalline ascorbic acid and of ascorbic acid from grapefruit

- 2 **Betty Jean Einbecker** (by invitation), **Lois Jackson** (by invitation), **Pauline Paul** (by invitation), and **Margaret A Ohlson**, *Department of Foods and Nutrition, School of Home Economics, Michigan State College, East Lansing*

Ascorbic acid in strawberries as measured by blood plasma of women following a test meal

- 3 **Daniel Melnick, Melvin Hochberg** (by invitation), and **Bernard L Oser**, *Food Research Laboratories, Inc, Long Island City, N Y*

Physiologic availability of the vitamins IX influence of ascorbic acid stabilizers in fruits and vegetables

- 4 **Mary Elizabeth Reid** (introduced by Helen T Parsons), *Division of Physiology, National Institute of Health, Bethesda, Maryland*

Role of gastrointestinal tract of the guinea pig in elimination of ascorbic acid given intraperitoneally

- 5 **Myra M Sampson and Louise M Potter** (by invitation), *Smith College*

The inter-relation of vitamin A and cholesterol in the liver of the albino rat

- 6 **W C Sherman** (introduced by W D Salmon), *Laboratory of Animal Nutrition, Alabama Polytechnic Institute, Auburn*

Relative gastro-intestinal stability of carotene and vitamin A and the vitamin A-sparing action of xanthophyll (*Biochem*)

- 7 **Louis L Madsen and I P Earle** (by invita-

tion), *Animal Husbandry Division, Bureau of Animal Industry, U S D A, Beltsville, Maryland*

The occurrence and chemistry of anasarca due to vitamin A deficiency in fattening beef cattle

- 8 **Dulal Pada Sadhu** (by invitation) and **Samuel Brody**, *Dairy Department, University of Missouri, Columbia*

Vitamin A and basal metabolism

- 9 **Bruce Kennelly** (by invitation) and **F W Quackenbush**, *Department of Agricultural Chemistry, Purdue University, Lafayette, Indiana*

Effects of oxidized lipids in the diet of the rat (*Biochem*)

- 10 **Joy E Criddle** (by invitation) and **Agnes Fay Morgan**, *Laboratory of Home Economics, University of California, Berkeley*

The effect of tocopherol feeding on the tocopherol and peroxide content of turkey tissues (*Biochem*)

- 11 **A T Milhorat and W E Bartels** (by invitation), *Departments of Psychiatry and Medicine, Cornell University Medical College, The Russell Sage Institute of Pathology and the New York Hospital, New York*

Effect of sugars, sugar alcohols and gastric mucin on utilization of tocopherol in muscular dystrophy

- 12 **E E Brown** (by invitation), **J F Fudge** (by invitation), and **L R Richardson**, *Division of Chemistry, Texas Agricultural Experiment Station, College Station*

Diet of the mother and brain hemorrhage in infant rats

## NUTRITION

Wednesday, 2 00 p m

CASINO, CONGRESS HOTEL

### General

- 1 **Julia O Holmes, L R Parkinson** (by invitation), **Anne W Wertz** (by invitation), **Beula V McKey** (by invitation), and **Lois Brow** (by invitation), *Agricultural Experiment Station, School of Home Economics, Massachusetts State College, Amherst*

Dental caries in the rat (*Mus Norvegicus*)

- 2 **E Potts Anderson** (by invitation), **J Knox Smith** (by invitation), **C A Elvehjem**, and **Paul H Phillips**, *Department of Biochemistry, University of Wisconsin, Madison*

The effect of milk on the incidence and extent of dental caries in the cotton rat

- 3 Philip Handler, *Duke University School of Medicine, Department of Biochemistry, Durham, N C*  
Influence of thyroid activity on liver lipids in choline and cystine deficiency
- 4 R W Engel (introduced by W D Salmon), *Laboratory of Animal Nutrition, Alabama Polytechnic Institute, Auburn*  
Relative effectiveness of choline, methionine, betaine, casein and egg albumen in preventing kidney hemorrhage
- 5 Grace A Goldsmith, *Nutrition Research Laboratory, Department of Medicine, Tulane University School of Medicine*  
The blood lactate-pyruvate relationship in various physiologic and pathologic states
- 6 Irma Rieckehoff (by invitation), Ralph Holman (by invitation), and George Burr, *Division of Physiological Chemistry, University of Minnesota*  
Effect of diet on polyethenoid fatty acids of rat tissues
- 7 Raymond Borchers and George L Peltier (introduced by C P Berg), *Departments of Agricultural Chemistry and Bacteriology, University of Nebraska, Lincoln*  
Molded feedstuff as a source of growth factors for chicks
- 8 Harold Blumberg and Aaron Arnold (by invitation), *Sterling-Winthrop Research Institute, Rensselaer, New York*  
Comparative biological availability of iron in the form of ferrous sulfate or ferric orthophosphate
- 9 Charles E Bills, Francis G McDonald (by invitation), William Niedermeyer (by invitation), and Melvin C Schwartz (by invitation), *Research Laboratory, Mead Johnson and Company, Evansville, Indiana*  
Survey of the sodium and potassium content of foods and waters by the flame photometer
- 2 Esther DaCosta (by invitation), R E Johnson, and G H Berryman (by invitation), *U S Army Medical Nutrition Laboratory, Chicago*  
Some effects of refeeding male albino rats after caloric restriction
- 3 R J Westfall (by invitation) and S M Hauge, *Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa, and the Department of Agricultural Chemistry, Purdue University, West Lafayette, Indiana*  
The protein efficiency of soybean flour as related to its trypsin inhibitor content
- 4 Dena C Cederquist (by invitation), Wilma D Brewer (by invitation), Norma Jean Radar (by invitation), and Margaret A Ohlson, *Department of Foods and Nutrition, School of Home Economics, and E J Benne (by invitation), Agricultural Experiment Station, Michigan State College, East Lansing*  
Nitrogen metabolism in college women
- 5 Ruth M Leverton and Doretta Schlaphoff (by invitation), *Nutrition Laboratory, College of Agriculture, Lincoln, Nebraska*  
Effect of protein, vitamin, and mineral supplements on blood regeneration in women donors
- 6 L B Pett, *Department of National Health and Welfare, Ottawa, Canada*  
The diagnosis of malnutrition
- 7 David K Bosshardt (by invitation), Winifred J Paul (by invitation), Kathleen O'Doherty (by invitation), and Richard H Barnes, *Department of Biochemistry, Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa*  
The influence of fat and carbohydrate calories on protein utilization
- 8 Alex Black (by invitation) and R W Swift, *Department of Animal Nutrition, School of Agriculture, Pennsylvania State College*  
Normal activity and economy of food utilization as affected by dietary fat
- 9 Margaret G Morehouse (by invitation), Bradley T Scheer (by invitation), and Harry J Deuel, Jr, *University of Southern California School of Medicine*  
The effect of dietary fat level on the physical capacity of rats during undernutrition
- 10 C F Wang (by invitation) and D M Hegsted, *Department of Nutrition, Harvard School of Public Health, and Department of Biological Chemistry, Harvard Medical School, Boston, Mass*  
The minimum protein requirements of adult dogs
- 11 Barnett Sure, *University of Arkansas, Fayetteville*  
The nature of protein enrichment of refined wheat flour with cultured yeast

#### NUTRITION BUSINESS MEETING

Wednesday, 4 00 p m

CASINO, CONGRESS HOTEL

#### NUTRITION

Thursday, 9 00 a m

CASINO, CONGRESS HOTEL

#### Amino Acids and Proteins

- 1 Joseph T Anderson (introduced by E S Nasset), *Department of Physiology and Vital Economics, University of Rochester*  
The biological value of amino acid mixtures in the rat

- 12 L V. Crowley (by invitation), R E Johnson, and G V Anderson (by invitation), U S Army Medical Nutrition Laboratory, Chicago  
Medical nutritional aspects of troops allowed free choice of any quantity of any item in a packaged ration

### NUTRITION

Thursday, 2 00 p m

CASINO, CONGRESS HOTEL

#### General

- 1 Margaret M Kaser (by invitation), Pauline Jones (by invitation), G Sydney McClellan (by invitation), Richard O Cannon (by invitation), and William J Darby, Departments of Biochemistry, Obstetrics, and Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee  
Preliminary observations on ascorbic acid and the vitamin B-complex during pregnancy and lactation
- 2 Margaret N Coryell (introduced by Icie G Macy), Research Laboratory, Children's Fund of Michigan, Detroit, Michigan  
Utilization of calcium pantothenate and biotin by lactating women
- 3 Helen Oldham, Bernice Blum Sheft (by invitation), and Thelma Porter, Department of Home Economics, University of Chicago  
Thiamine and riboflavin intakes and excretions during pregnancy
- 4 Robert R Spitzer (by invitation) and Paul H Phillips, Department of Biochemistry, University of Wisconsin, Madison  
Further studies in reproduction and lactation in rats fed natural rations
- 5 Walter C Russell, Klaus Unna, and Arthur E Teeri (by invitation), Department of Agricultural Biochemistry, New Jersey Agricultural Experiment Station, Rutgers University New Brunswick, Department of Pharmacology, University of Illinois Medical School, Chicago, and Department of Agricultural Chemistry, University of New Hampshire, Durham  
Growth and reproduction of swine on a purified diet
- 6 Barbara A McLaren (by invitation), D J O'Donnell (by invitation), and C A Elvehjem, Department of Biochemistry, University of Wisconsin and the Wisconsin Conservation Department, Madison  
Nutrition of rainbow trout
- 7 Ercel Eppright (by invitation), Robert McMillan (by invitation), and Pearl Swanson, The Nutrition Laboratory, The Foods and

Nutrition Section, Iowa Agricultural Experiment Station, Iowa State College, Ames  
Food habits and preferences of two groups of Iowa people

- 8 H B Pierce, R F Krause (by invitation), J H Browe (by invitation), Susan Merrow (by invitation) with the technical assistance of C A Newhall (by invitation), T H Harwood (by invitation), P D Clark (by invitation), R E Corley (by invitation), T B Tomasi (by invitation), J C Cunningham (by invitation), Milla E Newland (by invitation), Ruth Law (by invitation), Hattie Kaplan (by invitation), Anne Baker (by invitation), Elizabeth Paulsen (by invitation), Departments of Biochemistry, Medicine, and Anatomy, College of Medicine, University of Vermont, and the Vermont State Department of Health, Burlington  
Nutritional status of Burlington, Vermont children
- 9 Howard A Schneider (introduced by D W Woolley), Rockefeller Institute for Medical Research, New York  
The biological dimensions of an infection model suitable for nutritional experiment
- 10 Alberta Iliff (by invitation) and Robert C Lewis, Child Research Council and Department of Biochemistry, University of Colorado School of Medicine  
Interpretation of the basal metabolic rate of children of unusual body build
- 11 Howard F Root and Thorne M Carpenter, The George F Baker Clinic, New England Deaconess Hospital, Boston  
The respiratory quotients (R Q) of normal and diabetic subjects after breakfast and lunch

### NUTRITION

#### Papers Read by Title

- 1 James H Jones, Department of Physiological Chemistry, School of Medicine, University of Pennsylvania, Philadelphia, Pa  
Effect of feeding succinylsulfathiazole to rats on a diet low in choline
- 2 James H Jones, Claire Foster (by invitation), Werner Henle (by invitation), and Dorothy Alexander (by invitation), Departments of Physiological Chemistry and Pediatrics, University of Pennsylvania and Children's Hospital of Philadelphia, Philadelphia  
Effects of low potassium and low lysine diets on polyomyelitis in mice
- 3 Marinus C Kik, Department of Agricultural Chemistry, University of Arkansas, Fayetteville  
The lemon color reaction for thiamine in rats

- 4 **Marinus C Kik and Clarence G Leonard** *(by invitation)*, Department of Agricultural Chemistry, University of Arkansas, Fayetteville  
Photo electric control of rice milling
- 5 **J F McClendon and Wm C Foster** *(by invitation)*, Hahnemann Medical College, Philadelphia  
Goiter on an iodine free diet grown by hydroponics, and excluding any goiter nova
- 6 **L Mirone** *(by invitation)*, Leopold R Cerecedo, Department of Biochemistry, Fordham University, New York  
Growth and fertility of the male mouse on synthetic diets
- 7 **Vincent E Newe** *(by invitation)*, Leopold R Cerecedo, Department of Biochemistry, Fordham University, New York  
Growth of mice on highly purified diets containing mixtures of amino acids
- 8 **Albert J Sica** *(by invitation)*, Leopold R Cerecedo, Department of Biochemistry, Fordham University, New York  
Inefficacy of orotic and yeast adenylic acids as galactogogues in the rat
- 9 **Albert J Sica** *(by invitation)*, Leopold R Cerecedo, and Leonard J Vinson *(by invitation)*, Department of Biochemistry, Fordham University, New York  
The beneficial effect of milk on lactation in rats maintained on purified diets

## THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

### THIRTY-FIRST ANNUAL MEETING

MONDAY, May 19th, 1947

First (Joint) Session with The American Society for Experimental Pathology

9 00 a m (promptly)

(Papers Limited to Ten Minutes)

PALMER HOUSE, ROOM 14

- 1 **Michael Heidelberger**  
Presidential Address Science, Freedom and Peace
- 2 **Valy Menkin**  
Further studies on the leucocytosis promoting factor of exudates
- 3 **Max B Lurie and** *(by invitation)* **Samuel Abramson and Marvin J Allison**  
Constitutional factors in resistance to infection, the effect of estrogen on the pathogenesis of tuberculosis
- 4 **G M Mackenzie and K C Brewster** *(by invitation)*  
Determinants of virulence and avirulence in *Salmonella Typhimurium*
- 5 **William H Taliaferro and Lucy G Taliaferro** *(by invitation)*  
Reduction in immunity to malaria in chickens following treatment with nitrogen mustard
- 6 **James A Harrison and Elizabeth H Fowler** *(by invitation)*  
The exudative process shown by microorganisms in serologic reaction

- 7 **Louis Pillemer and William B Wartman**  
The action of crystalline tetanal toxin in white Swiss mice
- 8 **H F Deutsch, R A Alberty, L J Gosting, and J W Williams** *(by invitation)*  
Biophysical studies of blood plasma proteins Immunological properties of  $\gamma$  globulin from the plasma of normal humans
- 9 **F B Gordon, Frank M Schabel, Jr** *(by invitation)*, **Albert E Casey and William I Fishbein** *(by invitation)*  
Recovery of poliomyelitis virus from the throat during the incubation period
- 10 **Isabel M Morgan**  
Distribution of antibody in monkeys paralyzed from poliomyelitis virus infection
- 11 **Jacques Léger** *(by invitation)*, **George M C Masson and J Leal Prado** *(by invitation)*  
Factors influencing an anaphylactoid reaction in the rat (*Physiol*)

### JOINT SESSION OF THE FEDERATION

Monday, 1 45 p m

GRAND BALLROOM, STEVENS HOTEL

Program on p 3

TUESDAY, May 20, 1947

Second Session, 9 00 a m (promptly)

(Papers Limited to Ten Minutes)

PALMER HOUSE, ROOM 17

9 00 a m Business Meeting

9 15 a m

- 1 **Anna Dean Dulaney**  
Complement activity of human serum with especial reference to malaria
- 2 **Christine E Rice**  
Some factors governing the selection of a complement-fixation method
- 3 **John F Kent, Helen M Conway and Willie Mae Bodie** (*introduced by A F Coca*)  
A quantitative study of the complement-hemolysin relation
- 4 **Milton Gjelhaug Levine and Robert E Hoyt** (*by invitation*)  
Complement fixation in scleroma (Rhino-scleroma)
- 5 **Hans Neurath, Elliot Volkin** (*by invitation*), and **H W Craig** (*by invitation*)  
A preliminary survey analysis with the Euglobulin-Inhibition Method for the serologic diagnosis of syphilis
- 6 **Harold J Magnuson** (*by invitation*), **Harry Eagle**, and **Ralph Fleischman** (*by invitation*)  
The minimal infectious inoculum of *S Pallida* in rabbits, and its rate of multiplication in vivo
- 7 **L L Coriell** (*by invitation*), **C M Downs**, and **M P Clapp** (*by invitation*)  
Studies on Tularemia III Immunization of white mice
- 8 **Lloyd D Felton, Benjamin Prescott** (*by invitation*), **Gladys Kauffmann** (*by invitation*), and **Barbara Ottinger** (*by invitation*)  
Studies on immunizing substances in pneumococci XIV The distribution of specific polysaccharide in mouse tissues after injection of a "paralyzing" dose
- 9 **Mary Hewitt Loveless**  
Immunological studies of serum disease I Fluctuations in the precipitin nitrogen during four months following an acute serum reaction
- 10 **Henry R Eagle** (*by invitation*), and **Mary Hewitt Loveless**  
Evidence for the neutralization of antigen by reagin
- 11 **Noble P Sherwood, O O Stoland** (*by invitation*), **J S Kirk** (*by invitation*), and **D J Tenenberg** (*by invitation*)  
Anaphylaxis XVI Part II Studies on attempted passive sensitization of the dog with immune serum from rabbits
- 12 **Howard C Hopps and Tom S Gafford, Jr** (*by invitation*)  
Anti-reticulo-endothelial serum (anti-reticular cytotoxic serum) I Preparation and serologic studies

TUESDAY, May 20, 1947

*Thrd Session, 2 00 p m (promptly)*  
(Papers Limited to Ten Minutes)

PALMER HOUSE, ROOM 17

- 1 **Lewis L Engel and Raymond Randall** (*introduced by A F Coca*)  
The quantitative estimation of egg and chicken proteins in equine encephalomyelitis vaccine
- 2 **Lewis L Engel and Raymond Randall** (*introduced by A F Coca*)  
Some relations between equine encephalomyelitis virus (Eastern type) and normal host cellular constituents
- 3 **Orville J Golub**  
The interference phenomenon within the psittacosis-LGV group of viruses
- 4 **Randall L Thompson**  
The effect of metabolites, metabolite antagonists and enzyme-inhibitors on the growth of the vaccinia virus in Maitland type of tissue cultures
- 5 **I W McLean, Jr, Dorothy Beard** (*by invitation*), and **Joseph W Beard**  
Studies on the immunization of swine against infection with the swine influenza virus I Resistance following subcutaneous administration of formalized purified influenza virus
- 6 **Gilbert Dalldorf** (*by invitation*), **Sophia M Cohen**, and **Julia M Coffey**  
Resistance induced by vaccinia virus to pertussis infection in mice
- 7 **Joseph L Melnick and John T Riordan** (*by invitation*)  
Latent mouse encephalomyelitis virus as a contaminant
- 8 **Herald R Cox, James van der Scheer, Stewart Aiston** (*by invitation*), and **Emil Bohnel** (*by invitation*)  
Purification and concentration of influenza virus by means of alcohol precipitation
- 9 **Harry M Rose and Eleanora Molloy** (*by invitation*)  
Cutaneous reactions with the virus of herpes simplex

Business Meeting

Reading of Constitution

Election of Officers

PAPERS READ BY TITLE

- A D Hershey and J Bronfenbrenner**  
Effects of complement on the specific neutralization of bacteriophage  
Note The sessions of the Pharmacologic Society on Chemotherapy and Antibiotics will be held on Wednesday and Thursday morning 9 00 a m (Congress Hotel, Parlor A, B and C and English Walnut Room respectively)



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## FIELD RATION PROCEEDINGS

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# THE AMERICAN PHYSIOLOGICAL SOCIETY

## FIFTY-SIXTH ANNUAL MEETING

Chicago, Ill., May 18, 19, 20, 21, 22, 1917

(For possible corrections in any of the following abstracts see the next issue)

**Morphine-benzedrine analgesia in obstetrics.** *FRANK ANTON and STANLEY C. HARRIS* (introduced by John S. Gray). *Dept. of Obstetrics and Gynecology and Physiology, Northwestern Univ. Medical School.* Since it has been shown that Benzedrine potentiates morphine analgesia and that Benzedrine is a respiratory stimulant, it was considered rational to try this combination of drugs as a means of controlling obstetrical pain without depressing the infant.

Preliminary study was as follows: Forty-five minutes after the administration of 1 to 35 mg. of morphine subcutaneously, one horn of a gravid dog uterus (near term) was delivered. Thirty minutes later the second horn was delivered. No difference was observed between the pups of the two horns. They were very depressed, cyanotic and lived one hour or less. In 6 other pregnant bitches (near term) the first horn was delivered under the same conditions described above but 15 to 30 mg. of amphetamine were injected immediately after delivery of the first horn. Thirty minutes later the second horn was delivered.

The average interval from clamping of the cord to the first spontaneous inspiration was 14 seconds (range, 0-51 sec.) for the 13 pups delivered from the first horn. All of these pups died in 30 minutes or less. The first spontaneous inspiration of the 12 littermates delivered from the second horn (after amphetamine) occurred in an average of 1 second (range, 0-8 sec.). Some of these pups lived 5 hours unattended. Obviously all pups of this series were premature.

Clinically, 9 patients have been given morphine and Benzedrine, subcutaneously, for the relief of labor pain. Best results have been obtained with  $\frac{1}{2}$  grain of morphine and 5 mg. of Benzedrine. Analgesia was always obtained by the mother. The first spontaneous inspiration by infants born 1 to 7 hours after administration of the drug occurred an average of 42 seconds (0-97) after delivery of the child. Respiratory activity always preceded spontaneously and color and activity were considered good. [Aided in part by a grant from Smith, Kline and French Labs.]

**Forced water drinking.** *E. F. ADOLPH*, *Dept. of Physiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, New York.* When rats are given only food that is greatly diluted with

water, very large quantities are drunk. By varying the dilution, any intake of water may be secured up to 125 per cent of the body weight per 24 hours.

Whole milk arouses maximal drinking when its solids constitute 2.5 per cent in water. The intake of the mixture is on the average uniform from day to day for at least a week, and body weight is approximately maintained. In greater concentrations, substantially equal intakes of solids are obtained in all mixtures. In lesser concentrations the intake of solids diminishes markedly.

Urine output is correspondingly augmented. It is possible that capacity for excretion limits the maximal intake since the maximal excretory rates resemble those obtained by other means of forcing water excretion. Gradual increase in dilutions of the food offered lead to no greater ingestions, but experience with liquid foods is a necessary preliminary to copious intake of the most dilute mixtures.

Intake of diluted food is apparently guided by nutritive deficits. Water excesses are contracted in meeting the caloric requirements, up to the limit of excretory capacity. In the converse situation excesses of concentrated food are not ingested in any attempt to require more water. The pattern by which the deficit of food takes limited priority over the excess of water is part of an extensive and integrated series of coexisting patterns.

**An analysis of the contour of the femoral arterial pulse in hemorrhagic shock.** *ROBERT S. WILKINSON*, *Dept. of Physiology, Western Reserve Univ. School of Medicine, Cleveland, Ohio.* Central and femoral arterial pulses have been recorded optically in anesthetized dogs under relatively stabilized circulatory conditions during the course of a step-wise hemorrhage, during a period of maintained hypotension, and during the progressive circulatory shock that follows reinfusion of all withdrawn blood. By comparing pulse tracings obtained during the shock period with those obtained at equivalent pressures during the initial hemorrhage, it is possible to dissociate changes in pulse contour observed in shock from those which normally occur in simple hemorrhagic hypotension. Such comparisons reveal that the femoral arterial pulse exhibits an abnormal cataretic limb in shock, characterized by a more gradual fall of

pressure with a reduction in or obliteration of the dirotic waves

The lateral pressure pulse in the femoral artery is considered to represent a fusion of the transmitted pulse with a summated reflected wave and its oscillations. An analysis on this basis demonstrates that the abnormal contour of the femoral pulse in shock is due to an alteration in the form of the reflected wave, a change that appears to involve the addition of a low frequency reflection to the reflected components of high frequency that are observed normally. A possible interpretation of the appearance of this low frequency reflected component in shock would relate it to a process of vasodilation occurring in one or more discrete vascular beds. On the basis of other observations, the most likely site for such a dilation appears to be the arterial supply to the intestines.

**Hyperheparinemia the cause of the hemorrhagic disease produced by total body exposure to ionizing irradiation** J. GARROTT ALLEN *Univ of Chicago, Dept of Surgery*. When man or animal is heavily exposed to ionizing irradiations delivered over the entire body, multiple petechial hemorrhages appear and death may result from hemorrhage, infection or anemia or from the combination of these factors. Hemorrhage is prominent and may be the most striking of these phenomena. The hemorrhagic diathesis is accompanied by a prolonged bleeding and clotting time and by a severe thrombocytopenia.

The thrombocytopenia has been thought to be the cause of this hemorrhage, but because the clotting time was also prolonged it was suspected that some other factor might be involved. It was found that when the blood became incoagulable, as occasionally it did, it possessed anticoagulant properties since it delayed the clotting of normal blood. The anticoagulant suspected was heparin, since it was found that antiheparin substances (toluidine blue or protamine) restored the clotting time to normal both *in vitro* and *in vivo*. Moreover, the response of the clotting time to these antiheparin substances occurred regardless of whether thrombocytopenia was present, and after injection of these substances the platelet count was unchanged or still further reduced.

The serum calcium, phosphorus and magnesium were essentially unchanged. The prothrombin time was normal if the heparin-like substance was first neutralized. Fibrin formation was normal.

Attempts at isolating heparin from the blood of hemorrhaging irradiated dogs yielded an anticoagulant indistinguishable from heparin.

**Ability of human subjects to withstand "explosive compression"** SHANNON C. ALLEN *Bio-physics Branch, Aero Medical Lab, Air Materiel Command, Wright Field, Dayton, Ohio*. In preliminary attempts to determine permissible

limits of pressure fluctuation in pressurized cabins for fighter aircraft nine subjects were exposed to a series of 43 man-descents at extremely rapid rates from simulated altitudes. "Explosive compressions" were carried out in an altitude chamber either by suddenly breaking paper membranes stretched over a large diaphragm in the door or in the small lock by opening all available valves after reaching the desired altitude. Pressure increases ranged from 33.4 to 514.4 mm Hg and rates of from 0.2 to 8 p.s.i. per second were achieved. All subjects wore the standard AAF helmet and earphones and were not warned before the "explosion".

Two subjects reported temporary inability to clear the ears and one had temporarily blocked sinuses. All three recovered completely within 48 hours. Residual effects, in the form of increased difficulty in clearing ears and sinuses on subsequent flights, were reported only by the two subjects who underwent three descents from 30,000 feet in addition to descents from altitudes below 10,000 feet.

While it was impossible to determine absolute permissible limits of pressure increase from these data they are reported because the rates achieved are so far in excess of those previously believed possible to allow ready clearing of the ears and because they also far exceed the rates reported by Ivy (Northwestern Univ. Med. School Bull. 16: 254, 1942) to cause significant circulatory and respiratory changes in anaesthetized dogs.

**Dissociation of T-1824 albumin by synthetic detergent** THOMAS H. ALLEN (introduced by Magnus I. Gregersen) *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* Optical density values of the dye, T-1824, in 0.85 per cent NaCl when plotted as a function of increasing concentration of human serum albumin ( $0$  to  $2 \times 10^{-5}$  M) can be described by a smoothly descending, then rising curve. The minimum occurs where the ratio of moles albumin dye = 1:10, which is the approximate binding capacity as shown by Rawson (1943) using an electrophoretic method. In the presence of 0.015 per cent Aerosol OT (dioctyl sodium sulfo-succinate) the curve is shifted to the right and upwards.

Both the detergent and dye probably combine with the same chemical parts of the albumin molecule. In an albumin-dye-detergent system the occurrence of "free dye" would be related to the dissociation constants of the several albumin compounds. The "splitting" of the dye-albumin compound by detergent with the consequent liberation of dye can be demonstrated with Cellophane strips. At 37° C. the time course of loss in optical density of the liquid phase (or uptake of dye by Cellophane) becomes more rapid and complete as the albumin concentration is decreased. With the

addition of Aerosol OT this inverse relationship is more pronounced and extends through a wider range in albumin concentration

It seems possible that a similar splitting of dye from protein is involved in dye excretion by the liver. Hence, it has become of interest to investigate the effects of naturally occurring detergents on the dye albumin linkage

**Effect of three bilateral cerebral lesions on correct cutaneous conditioned differential responses of dog's foreleg** WILLIAM F. ALLEN *Dept of Anatomy of the Univ of Oregon Medical School, Portland* Lesion A destroyed the cerebral cortex between the posterior and ansate sulci (Woolsey's cutaneous area I for leg, trunk and arm). Lesion B eliminated the coronal gyrus (Woolsey's area I for face). Lesion C deleted the basal portion of the cerebellar gyrus (Woolsey's cutaneous area II). The positive and negative conditioned reflex stimuli for both sets of differential responses were (1) stroking the back with a brush once per second, with and against the grain, (2) stroking the back with the grain, once and 3 times per second.

**Results** Lesion A permitted immediate return of correct conditioned differential responses with both sets of stimuli, but confirming Bard, abolished the cutaneous plethoric reflex. If the foreleg motor cortex on the opposite side was injured the foreleg flexion of all joints was changed to a stiff leg movement originating from the shoulder or trunk. Lesions A and B also permitted immediate return of these correct responses, but delayed considerably the number of daily sessions required to produce a perfect score. Present indications are that if lesions A, B and C do not permanently abolish these correct conditioned differential responses, they prevent their reestablishment for many more tests than were previously reported for lesion C. In one of these dogs the barking conditioned reflex described in this Proceedings was substituted for the foreleg reflex.

The effects of lesions C or A, B and C consisted chiefly of inability to withhold the foreleg response for the negative conditioned stimuli (absence of correct inhibition).

**Bark used for the response in a positive conditioned reflex** WILLIAM F. ALLEN *Dept of Anatomy of the Univ of Oregon Medical School, Portland* This response was readily established and successfully used in place of the foreleg response in one dog for conditioned differential responses with 2 different sets of general cutaneous stimuli. It came into use as follows: After destroying Woolsey's cutaneous areas I and II of the left cerebral hemisphere, the right foreleg was sufficiently paralyzed from injury of the motor cortex to prevent flexion of the right foreleg from the conditioned stimulus used, namely, stroking the back with a brush once per second with the grain. Long before

the positive conditioned reflex could be elicited from the right or uninjured motor cortex, one or more barks immediately followed each application of the cutaneous stimulation. After this barking reflex became firmly established there was no difficulty in obtaining 2 different negative conditioned reflexes (absence of a bark) from stroking the back once per second against the grain and from stroking the back 3 times per second with the grain. This culminated in the perfect establishment of 2 different sets of cutaneous correct differential responses in which the positive barking reflex was paired with each of the above mentioned negative conditioned reflexes. Following elimination of cutaneous areas I and II from the right or opposite hemisphere, correct conditioned differential responses were not reestablished for the with and against tests during 1100 trials or later during 500 trials for the slow and fast brush tests.

**The peripheral effect of curare on skeletal muscle fasciculations** BERNARD J. ALPERS, RICHARD G. BENNY, and FRANCIS M. FORSTEN (introduced by M. H. F. Friedman) *Dept of Neurology, Jefferson Medical College, Philadelphia, Pa.* Previous investigations on the origin of fasciculations in skeletal muscle have demonstrated that these phenomena are not effected by pharmacologic block of nerve roots or peripheral nerves. Section of peripheral nerve does not abolish fasciculations immediately. The incidence of fasciculations is altered by drugs, especially curare and prostigmine, presumably acting at the myoneurial junction. Recent evidence suggests that curare has a central as well as peripheral action. The present experiments were undertaken to determine whether the curare effect on fasciculations was central or peripheral in location.

The effects of curare on fasciculations were determined (1) by intra arterial injection of curare in an extremity with venous return occluded, (2) by intravenous injection of curare with the arterial supply of the opposite limb occluded, and (3) by intravenous injection of curare with the venous return of the opposite extremity occluded. In experiment (1) fasciculations decreased first in the limb with the intra arterial injection and venous occlusion. In experiment (2) fasciculations were maintained in the extremity with the arterial occlusion, and in experiment (3) fasciculations persisted longer in the extremity with venous occlusion.

From these results it is concluded that the curare decreases or abolishes fasciculations by peripheral action and not by central action. Venous stasis decreases the effect of curare on fasciculations.

**The effect of various substrates on the oxygen consumption of heart muscle of the adrenalectomized rat** CLIFFORD A. ANGERER and JORGE

GONZALEZ Q (by invitation) *Dept of Physiology, The Ohio State Univ, Columbus* Hearts were obtained from male white rats which weighed from 80-120 grams and were starved from 18-21 hrs before the experiment. All adrenalectomized rats were used postoperatively any time after the fourth day but not when in the "acutely insufficient state." The hearts from ca 6-10 rats were sheered at a predetermined thickness of 0.6 mm and were pooled in a known volume of Krebs Ringier solution. This solution was buffered at pH 7.4 with  $\text{Na}_2\text{HPO}_4$ . Approximately 100 mg samples of tissue were immersed in 2.5 cc Krebs solution. Oxygen uptake was determined by Fenn technique, in an atmosphere of pure oxygen and at a temperature of 37.5°C. The final results were expressed as  $\text{QO}_2 = -\text{mm}^3 \text{O}_2 \text{ consumed/mg (dry wt) heart tissue/hr}$ . With the exception of tissue  $\text{QO}_2$  for normal and adrenalectomized animals, which bear comparison, the studies were generally made following an initial run of 1 hour before dumping of the respective substrate from the side arm. Thus it is not valid at this time to compare the per cent change in  $\text{QO}_2$  due to a given substrate with the per cent change in  $\text{QO}_2$  for the same substrate in a different experimental group of rats. The results are as follows: Normal rats, Strain "A",  $\text{QO}_2 = 4.73$  and "B" = 4.97, glucose, -8%, succinate, +181%, pyruvate, +34%; lactate, -11%, Adrenalectomized rats, Strain "A",  $\text{QO}_2 = 6.23$ , and "B",  $\text{QO}_2 = 6.00$  (which is an increase over the controls of 32% and 21% respectively), glucose, -4%, succinate, +617%, pyruvate, 30%, lactate, +19%.

**Function in the developing liver** PHILIP B ARMSTRONG *Syracuse Univ College of Medicine* Our knowledge of differentiation in developing embryos is derived almost exclusively from morphological research. Function in development has received rather scant consideration although one might anticipate that physiological studies could reveal functional differentiation before there were detectable morphological changes. Such appears probable in the developing salamander liver. If certain dyes are injected into developing salamander embryos in an appropriate stage of development, the injected dye, after a period of hours, is seen exclusively in the developing liver and gastrointestinal rudiments. The liver rudiment when it first concentrates the dye has as yet none of the special histological features of the adult liver. There are no cords of liver cells or bile capillaries and no sinuses nor has the gall bladder yet formed. The liver rudiment is a thickened plate of cells lining the anterior wall and floor of a ventral diverticulum from the foregut. With subsequent development, the bile capillaries, sinuses, and gall bladder form concurrently and the dye in the par-

enchymal cells is eliminated into the early bile capillaries.

Apparently during embryonic development of the liver in the salamander, dye elimination is resolved into two processes, first, the concentrating of the dye in the liver rudiment and second, the elimination of the dye from the parenchymal cells after the formation of the bile capillaries. In the first of these processes we see the differentiation of function unaccompanied by any detectable histological specialization.

**The relationship between the renal tubular reabsorptive capacity for phosphate and glomerular filtration rate** J. L. AYER (by invitation), W. A. SCHIRSS (by invitation) and R. F. PITTS *Dept of Physiology, Syracuse Univ College of Medicine, Syracuse, New York* It is common practice to express the capacity of the renal tubules to reabsorb materials from the urine in terms of milligrams or millimols per 100 ml of glomerular filtrate. Such a mode of expression tends to bring into agreement data obtained on animals of various sizes and functional capacities. One obvious reason for this correlation between glomerular function and tubular function in different animals is the evident morphological correlation between the diameters of the individual glomeruli and the masses of their attached tubules. It does not necessarily follow that in a given animal functional increases in filtration rate are accompanied by equivalent functional increases in tubular reabsorptive capacity. The reabsorption of chloride and of bicarbonate is so correlated with filtration rate, the reabsorption of glucose and of vitamin C is fixed and independent of filtration rate. Experiments were performed on two dogs in which phosphate Tm was assessed at a series of filtration rates, varied by alteration of the protein content of the diet. Such physiologically induced changes in filtration rate are without effect on the tubular reabsorptive capacity for phosphate. Thus, the mechanism for the reabsorption of phosphate is functionally more closely related to that for the reabsorption of glucose than it is to that for the reabsorption of chloride and bicarbonate. [Aided by grants from the U. S. Public Health Service and the John and Mary R. Markle Foundation.]

**The vestibular nuclei as an excitatory mechanism for the cord** L. M. N. BACH (by invitation) and H. W. MAGOUN *Dept of Anatomy, Northwestern Univ Medical School, and Dept of Physiology, Tulane Univ Medical School* Recent demonstration of a facilitatory mechanism in the brain stem tegmentum led to examination of its relationship to the vestibulo-spinal system and to scrutiny of the latter's role of contributing excitatory influences to spinal motor activity.

Electrical stimulation of the vestibular nuclei did not facilitate reflexly or cortically induced

movement and such facilitation from tegmental stimulation was unimpaired by destruction of the vestibular nuclei

In decerebrate cats, unilateral destruction of the vestibular nuclei or interruption of the ventral funiculus of the cord, containing vestibulo spinal connections, abolished extensor rigidity and reduced phasic reflexes on the injured side, similar but less pronounced results followed tegmental lesions or interruption of the lateral funiculus of the cord, in which descending facilitatory connections from the tegmentum are concentrated. In cats with spasticity from bilateral removal of the perineurte cortex, and in which the length of the brain stem tegmentum remained intact, unilateral destruction of the vestibular nuclei only partially reduced extensor hypertonus and did not diminish hyperactive tendon reflexes or clonus.

The pronounced reduction of rigidity and phasic reflexes which follows vestibular nuclear destruction in the decerebrate animal is evidently dependent not alone upon the vestibular lesion but upon the additional circumstance that all but the bulbar part of the tegmental facilitatory mechanism is eliminated by decerebration. At present, tegmental and vestibular systems each appear to contribute excitatory influences to the cord, over distinct paths, and to an extent the former seems more concerned with phasic and the latter with postural activity.

**Ultraviolet action spectra** ALBERT BACHMANN, *Dept of Physiology, Univ of Illinois, Chicago Colleges*. A study of the ultraviolet action spectra is of interest not only from theoretical points of view, but also for practical purposes, such as the proper evaluation of ultraviolet generators.

Three ultraviolet spectral areas produce erythema. Maximal reactions occur at 254, 297 and 360 m $\mu$ . The erythemagenic efficiency is lowest for the area 360 m $\mu$ . The 254 m $\mu$  erythema exhibits the flattest gradation curve, the margin of safety is greatest for this wavelength, blistering is practically impossible.

Pigmentation occurs in the same 3 areas. Wave length 254 m $\mu$  is most efficient, but the pigmentation is of very short duration. The area around 360 m $\mu$  is least efficient, but the pigmentation lasts over a considerable time period.

The antirachitic effect starts below 313 m $\mu$ , shows several maxima corresponding to the provitamin D absorption curve and declines gradually toward short wave ultraviolet.

The germicidal efficiency is maximal around 265 m $\mu$ . It falls sharply toward longer and gradually toward shorter wavelengths.

The carcinogenic effect extends from 290 to 340 m $\mu$ .

The Council on Physical Medicine of the American Medical Association defines generators of the

290 to 313 m $\mu$  range as "sunlamps" and considers these as the only ultraviolet generators "acceptable" for home use without medical supervision. Unfortunately, this specification rules out the most germicidal and pigmenting rays, moreover, it selects the spectral range which permits easy burning and blistering and may produce skin cancer.

The proper spectrum for home lamps should contain the 260 and 360 m $\mu$  areas without the 300 m $\mu$  range.

**Hepato-renal factors in circulatory homeostasis** XIV **Vascular effects of acute renal occlusion in dogs** S. BAIZ (by invitation), B. W. ZWEIFACH and EMMETT SNODD, *Dept of Medicine, Cornell Univ Medical College and The New York Hospital, New York City*. The Taquini experiment, in which complete renal ischemia of from 4 to 6 hours duration results in a blood pressure rise of from 20 to 30 mm Hg, has been used as evidence for a renal factor in hypertension. In our experiments, renal ischemia for such prolonged periods did not result in the appearance in the blood stream of the vaso excitator principle (VEM), which we have observed to occur in hypertensive dogs (Goldblatt clamp). This was determined by taking blood samples during the period of transient hypertension following the release of ties about the renal artery, and assaying the blood for vasotropic activity by the rat meso-appendix technique. Observations were also made on the reactivity of the peripheral blood vessels in the omentum of the dog following varying periods of acute renal occlusion.

No vascular hyper-reactivity was detected after renal occlusion of 4-6 hours. Renal ischemia of less than 3 hours, although producing a much smaller blood pressure rise, resulted in the development of a pronounced hyper reactivity in the omental arterioles and precapillaries and in the appearance of VEM in the blood. This vaso-excitator effect persisted for at least 90-120 minutes, the period of observation, whereas the blood pressure effects were of relatively brief duration (ca 15 minutes). The VEM effect was transferable to test rats. When equivalent blood pressure rises were induced by angiotonin, no vaso excitator activity was demonstrable in the blood. [Aided by grants from the Josiah Macy, Jr Foundation and the Eli Lilly Co.]

**Effect of deficiency in anti-stiffness factor on relative arterial occlusion pressure of guinea pigs** ALICE M. BAHR and ROSALIND WULZEN, *Dept of Zoology, Oregon State College*. To determine the effect of anti stiffness factor on relative arterial occlusion pressure (AOP) of guinea pigs, the femoral artery was occluded as follows. An animal was stretched on a holder. A rubber wedge attached to the piston of a vertically supported hypodermic syringe was placed transversely across



the femoral artery at the point where the artery crosses the medial aspect of the femur. A sphygmomanometer was connected to the syringe. Pressure was applied by the sphygmomanometer bulb until no pulse could be felt in the femoral artery below the point of occlusion. The registered pressure necessary to occlude the artery was read as AOP. Each reading was the average of five determinations. The deficient diet consisted of 20% skim milk powder in water. A full assortment of water soluble and fat soluble vitamins and salts was administered and the animals were bedded in wheat straw.

143 animals were used. The mean AOP for 42 stock animals was found to be  $29.714 \pm 0.527$  mm Hg. 53 animals maintained on the deficient diet for eight months to two years had a mean AOP of  $42.452 \pm 0.683$  mm. The difference in mean values for the stock animals and these older deficient animals was 14 times the probable error and hence was statistically significant. 48 animals maintained on deficient diet  $2\frac{1}{2}$  months gave a mean AOP of  $32.125 \pm 0.536$  mm.

Using our method we found that guinea pigs fed diet deficient in anti-stiffness factor for a sufficient time had significantly higher relative arterial occlusion pressure than control animals.

**Depth of penetration of nebulized substances in the respiratory tree.** GEORGE P. BAIN, JACK Q. SLOAN, and MARSHALL BRUCER (introduced by Eric Ogden). *Dept. of Physiology, Univ. of Texas, Galveston, Texas and Scott and White Clinic, Temple, Texas.* The fate of nebulized substances in the respiratory tree was studied in mice, rats, and rabbits lightly anesthetized with pentobarbital sodium (Nembutal). A commercial nebulizer was used to obtain a fine mist of a 50% India ink suspension, a 1% gentian violet solution, and a 1% ferrous ammonium sulfate solution. The size of the nebulized droplets was directly observed to include particles less than one micron in diameter. The mist was introduced to the respiratory tree by a glass tube placed in the oral pharynx. Gross and microscopic observations were made of the respiratory tree immediately after the animal had been exposed to the mist for fifteen minutes.

Preliminary observations indicate that the particles were deposited in the larynx in large amounts. Particles have been observed as far down as the large bronchioles, but in extremely minute quantities. In two animals, gentian violet was noted in a few alveoli near the visceral pleura, but this requires further confirmation. No carbon or iron was demonstrated below the level of the larger bronchioles.

**Delimitation of central nervous mechanisms involved in motion sickness.**<sup>1</sup> PHILIP BARD, C. N.

WOOLSEY, R. S. SNIDER (by invitation), V. B. MOUNTCASTLE (by invitation) and R. B. BROMLEY (by invitation). *Dept. of Physiology, The Johns Hopkins Univ. School of Medicine, Baltimore, Md.* The dogs selected for these experiments had regularly vomited on being exposed, at weekly intervals, to the motion of a swing. Each was studied during long postoperative periods while in good health.

Bilateral temporal lobectomy, removal of both frontal poles (containing somatic motor and sensory areas) or ablation of all neocortex except one or both frontal poles did not significantly alter susceptibility to the emetic action of motion. The effect of complete decortication was not determined.

A dog, which had vomited within 4-10 minutes in seven tests, was decerebrated by removing, after ablation of caudal cortex, a wedge of tissue rostral to a plane passing from the anterior colliculi to a level just behind the mammillary bodies. Between the twenty-sixth and fifty-third postoperative days it was swung five times and on each occasion emesis, preceded by typical prodromal signs, occurred within 3-9 minutes.

After uncomplicated removal of the entire cerebellum a highly susceptible dog failed to vomit or show any premonitory symptoms in fifteen tests of 60 minutes carried out during a survival period of seventeen months. In three dogs a similar result was obtained by removing only pyramis, uvula and nodulus. Removal of only pyramis and adjacent folia of uvula or extirpation of all vermis between primary fissure and pyramis in no way affected susceptibility. The dogs rendered immune to the emetic effect of motion vomited in response to eating spoiled food or to a minimal dose of apomorphine.

**Venous pressure and cutaneous reactive hyperemia in exercise and other circulatory stresses.** A. C. BARGER and L. H. SMITH, JR. (introduced by E. M. Landis). *Dept. of Physiology, Harvard Medical School, Boston, Mass.* Peripheral venous pressure and cutaneous reactive hyperemia were studied during mild and vigorous exercise on the treadmill, using successive 10-minute periods at increasing work rates in 8 normal subjects ranging in age from 20 to 45 years. Venous pressure, measured directly in the forearm or hand by a saline manometer, began to fall slightly when walking started at  $1\frac{1}{2}$  and 2 miles per hour on the level. Walking on a 5° grade at 3 miles per hour elevated venous pressure slowly to between 25 and 50 mm. water above resting values. Walking on a 10° grade at 3 miles per hour increased the venous pressure still further to maxima reaching 70 to 150 mm. water above resting values.

<sup>1</sup> Much of this work was done under contract, recommended by the Committee on Medical Research, between the Office of

The appearance and persistence of cutaneous reactive hyperemia (see abstract by Greenwood, DiPalma and Stokes) remained within normal limits until late in exercise. Eventually, in all subjects so far tested, the "threshold" rose suddenly (75 to 200 per cent) as did the "clearing time" (75 to 330 per cent). The exact timing of these changes during exercise varied from subject to subject but generally accompanied the approach of exhaustion. These findings, together with transient fall of skin temperature in some subjects, indicated shunting of blood away from the skin despite rising rectal temperature and increasing need for heat dissipation. It appears that the cutaneous vessels constrict during the circulatory stress of exercise but this response appears only in the later stages as exhaustion approaches. To compare the effects of other types of circulatory stress on reactive hyperemia the same subjects were tested (a) while standing on a tilt table at 70°, and (b) while supine with venous congestion of 3 extremities. Under these conditions the responses of the cutaneous vessels changed in the same direction but only in some subjects and were generally less conspicuous than in exercise. Tilting elevated "threshold" by 40 to 90 per cent and did not affect "clearing time", pooling of venous blood elevated "threshold" in some instances by 15 to 200 per cent and "clearing time" by 15 to 50 per cent.

**Effect of dinitrophenols on rat thyroids** S. B. BARKER, *Dept. of Physiology, State Univ. of Iowa, Iowa City*. Rats rendered hypothyroid by thiouracil have been shown to exhibit a diminished metabolic response to the dinitrophenols. In contrast, animals made hyperthyroid by administration of desiccated thyroid substance show increased sensitivity to dinitrophenols. It was thought of interest to determine whether any activation of the thyroid gland by the dinitrophenols could be detected.

Eight male albino rats were given 4 injections per day of 10-15 mg of dinitrophenol or dinitro-*o*-cresol per kg body weight. This was continued for 14 days. At the end of this time, the rats were found to give essentially the same increase in oxygen consumption following a single injected dose of drug as at the start of the series of injections. Although calculations indicated that the metabolic rate had been elevated 20-45% on the average throughout each day, no effect was detectable on weight or histological appearance of the thyroids.

**Headache—etiology and treatment** BRODA O. BARNES, *Kingman, Arizona*. If thirteen patients consult a doctor, one of them will complain of severe headache. Hence, headache is one of the most frequent ailments of modern man. It may vary in intensity from a moderate discomfort to the severe migraine which may totally disable the individual for two or three days each month.

The present report is concerned with an eight year study of this problem in over one hundred patients suffering from either severe headache or migraine.

Of the many theories advanced for the etiology of headache, raised intracranial pressure appears the most plausible. Fatigue seems to play a dominant part in initiating headache. Fatigue may alter permeability and lead to accumulation of excessive extracellular fluids. Swelling of the feet is quite common during excessive fatigue and it seems reasonable that the brain should also swell causing undue pressure in the rigid cranium, with pain resulting. All sufferers from migraine know that after a few days of bedrest, the attack subsides.

Regarding treatment, the patient desires an effective, inexpensive, convenient remedy which interferes as little as possible with his daily routine. Each patient comprising this report was carefully studied as to his history, physical examination, and laboratory findings which included either basal metabolism or basal temperatures. Practically all cases presented evidence of thyroid deficiency, and hence, were treated with thyroid extract. Within thirty days after medication was started, a marked decrease in both frequency and severity has been the rule. Many cases of migraine have been completely relieved.

**Transient phase boundary potentials which resemble the nerve impulse** T. C. BARNES, *Dept. of Physiology and Pharmacology, Hahnemann Medical College and Hospital of Philadelphia*. Non-polarizable Ag/AgCl electrodes connect the saline phase on each side of the oil cell previously described (Barnes and Beutner, *Science* 104: 569, 1946) to leads of an electroencephalograph. The addition of acetylcholine to one side of the oil layer produces a fluctuating potential not detected by the old potentiometric method of measuring phase boundary potentials. One c.c. of saline as control is added from a clamped pipette (this procedure sometimes produces small positive wave probably unequal distribution of sodium in the oil due to stirring effect). The addition of a second c.c. of saline containing one milligram of acetylcholine (to 200 c.c. of saline on one side of the oil) produced a negative wave of several millivolts lasting 0.2 to 0.5 seconds. This concentration of acetylcholine in saline in contact with guaiacol does not produce a permanent phase boundary potential (potentiometric measurements made before and after the acetylcholine was added showed no change). The highly sensitive benzoate nitrobenzene system was not used (large potentials block amplifier). On guaiacol saline one mg of acetylcholine gives small potential waves that are shorter than the time constant of the amplifier. A simultaneous recording DC AC EEG is under construction for this work. In living nerve a trace of acetylcholine probably produces a transient

potential at the lipid layer (no esterase required) for impulse formation

**Outline of a method of procedure in electroencephalography** T C BARNES *Dept of Physiology, Hahnemann Medical College and Hospital of Philadelphia* A pneumogram may show irregular respiration suggesting kinesthetic laryngeal component of auditory mental imagery and high alpha index (Golla, J Ment Sc 89 216, 1943) Sighing respiration suggests neurosis and beta waves Lowenfeld's (Am J Psychol 58 100, 1945) tests for visual and haptical (kinesthetic) mental imagery aid in explaining low alpha index The Hunt Minnesota psychological test for cerebral damage (J App Psychol 28, No 2, 1944) correlates with abnormal waves Comparison of design pair association with word pair association helps in estimating visual imagery and low alpha index Malamud's (J App Psychol 28, No 2, 1946) claim that normals five false Hunt positives was not confirmed The Cerebral Hyperventilation Index (J Psychol 22 67, 1946, Fed Proceed 5, 5, 1946) is slightly modified as follows—Blood sugar below 115 rates plus 4, 115–130 plus 2, 135–150 minus 2 and above 150 minus 4 Skin temperature fall of  $1^{\circ}\text{C}$  or less rates plus 1 and more than one-degree plus 3 Decreasing susceptibility to acapnia with age required correction factors, ages 5 to 9 years get plus 7, 10 to 14 plus 5, 15–19 plus 3, 20–24 plus 1, 25–29 zero, 30–34 minus 1, 35–39 minus 2, 40–44 minus 3, 45–49 minus 4, 50–54 minus 5, over 55 minus 6 Vital capacity, effort and degree of EEG abnormality scores remain as before

Bell Adjustment Inventory gives good personality scores for normal EEG in acapnia Stereotyped Rorschach responses correlate with delta waves

**Electrical action of anticonvulsant drugs** T C BARNES *Depts of Physiology and Pharmacology, Hahnemann Medical College of Philadelphia* The theory that the nerve impulse is an electrical phase boundary potential of acetylcholine (Barnes and Beutner, Science 104 569, 1946) suggests that grand mal is produced by excess brain acetylcholine (Barnes, J Psychol 22 67, 1946) Dilantin and sodium phenobarbital have positive potentials that neutralize acetylcholine potential Guaiacol shaken in contact with 0.0027 M dilantin in saline had a resistance of  $75 \times 10^4$  ohms compared with  $128 \times 10^4$  ohms for guaiacol shaken with saline and  $28 \times 10^4$  ohms for guaiacol shaken with 0.0027 M acetylcholine Application of the Nernst equation  $0.058 \times \log$  conductivity increase produced by dilantin in saline compared with saline alone (1.78 fold decrease in resistance) gives  $0.058 \times 0.25$  or 14.5 millivolts (measured value of 18 millivolts positive produced by 0.0027 M dilantin in contact with guaiacol) Sodium phenobarbital gave similar conductivity and e m f results Guaiacol shaken

with 0.0027 M sodium phenobarbital in saline had a resistance of  $7.7 \times 10^5$  ohms compared with  $14 \times 10^5$  ohms for guaiacol control shaken with same sample of saline 0.5% tridione gave no potential at an oil interface and did not alter the resistance of guaiacol when shaken together Thus tridione does not produce a positive potential to neutralize the negativity of acetylcholine (hence it is not effective in grand mal) and probably acts chemically in petit mal [Aided by a grant from the Plotz fund]

**Mechanism of action of prostigmine** T C BARNES *Depts of Physiology and Pharmacology, Hahnemann Medical College of Philadelphia* Confusion concerning the mode of action of prostigmine arose from the erroneous statement of Nachmansohn (J Neurophysiol 9 9, 1946) that quaternary amines are insoluble in lipid and from the failure of McKen Cattell (Fed Proc 5 199, 1946) to consider the physical properties of prostigmine which can explain its action apart from toxicity to esterase Prostigmine produces three times electrical phase boundary potential of acetylcholine (Barnes, Anat Rec 94 No 4, 1946, Arch Int Pharmacodyn in press) Guaiacol resembles protoplasmic lipid (conductivity, similar lipid solvent action, selectivity for K), (Osterhout, J Gen Physiol 15 667, 1932) 20 c.c. of guaiacol were shaken with 100 c.c. of 0.0027 M prostigmine methylsulfate in saline for 5 hours and the conductivity of the oil was  $4.0 \times 10^4$  ohms compared with  $19.4 \times 10^5$  ohms for oil shaken with saline and  $31 \times 10^4$  ohms for oil shaken with 0.0027 M acetylcholine in saline The dry oil was  $8200 \times 10^4$  (shaken with  $\text{H}_2\text{O}$ ,  $1800 \times 10^4$ ) According to the Nernst equation the e m f is  $0.058 \times \log$  conductivity increase of oil produced by prostigmine compared with saline alone (48 fold increase) or  $0.058 \times 1.68$  equals 97 mv which is close to measured value of 85 mv for 0.0027 M prostigmine in contact with the oil 0.0005 M prostigmine produces 17 mv negative on frogs sciatic in glucose (technique of Netter Pflügers Arch 218 310, 1927)

**Use of pentothal in electroencephalography of babies** T C BARNES and MARIE D AMOROSO (by invitation) *Dept of Physiology, Hahnemann Medical College and Hospital of Philadelphia* Previous reports (Barnes, Hahnemann Mo 81 239, 1946, Fed Proc 5 5, 1946, Anatom Rec 96, No 4, 1946, Arch Pediatrics, in press) described the electroencephalograms of infants under pentothal 20 mg per lb rectally usually in 15 c.c. of water (method of Dr H S Ruth, Dept of Anesthesiology, Hahnemann Hospital of Philadelphia) We have taken 54 EEGs of 48 babies age 2 months to 5 years Pentothal was given 44 times In 38 cases the effect of pentothal gave anesthesia satisfactory for electroencephalography Anesthesia was too light in 6 cases (partly a result of evacuation

of pentothal solution) Approximately 75% of the EEGs were of clinical value 6 channel simultaneous recording is essential The best line way in infants EEGs is so prominent that we have a combined DC and AC EEG under construction The simultaneous recording of fluctuating and slow potential changes may solve the difficulty of interpreting infantile EEGs Walter's classical paper (*Lancet* 231 2, 305, 1936) described base line fluctuations due to electrical changes in the brain The fast pentothal waves (100 microvolts 20 per second) appear on normal areas of the baby's cortex and aid in localization of lesions The baby falls asleep usually about 6 minutes after pentothal is given and the fast pentothal waves gradually reach maximum voltage in about 15 minutes The pentothal waves do not entirely obscure spike and dome waves (found in petit mal, grand mal, trauma, syphilis)

**Bioelectrical studies of fatigue III** Further studies of alleged mental fatigue in students T C BARNES and MARI D AMOROSO (by invitation) *Dept of Physiology, Hahnemann Medical College and Hospital of Philadelphia* Previous reports (*Fed Proceed* 5 5, 1946, *J Psychol* 22 181, 1946) described electroencephalograms of students taken at 8 A M and 5 P M of a typical day of classes No statistically significant EEG signs of mental fatigue at 5 P M were found Grüttner (*Arch Psychiat Nervenkr* 111 652, 1940) found loss of regular alpha in fatigued persons It is of interest to note that recently Kornmüller (see Alexander *Dept Commerce Report* No 359, p 23) also found discontinuity of alpha in fatigue We have completed EEG fatigue studies on 47 students but no significant loss of alpha occurred after a day of classes The Bell Inventory Personality scores show no correlation between alpha index and retiring or aggressive personalities (correlation with Cerebral Hyperventilation Index is described in another abstract in these Proceedings) More elaborate personality tests or more severe types of work may be correlated with alpha index Alpha waves indicate slight cerebral vasoconstriction (Darrow, *J Neurophysiol* 8 449, 1945) Students with no alpha showed alpha waves in the first minute of deep breathing (cerebral vessels slightly constricted but not sufficiently to produce delta waves) In several students spindles of alpha waves occurred with the same frequency as quiet respiration (subject recumbent and relaxed) but this correlation was the same A M and P M In several persons the number of alpha spindles exceeds the number of respirations

We conclude that the eight hour day of classes does not produce severe mental fatigue and should be lengthened

Electroencephalograms correlated with scores of the Bell adjustment inventory for personality

T C BARNES and MARI D AMOROSO (by invitation) *Dept of Physiology, Hahnemann Medical College and Hospital of Philadelphia* EEGs taken without analysis are unsatisfactory Walter's Analyser (*J Neurol Neurosurg Psychiat* 7 119, 1944) is promising Another method (Barnes, *Fed Proc* 5 5, 1946, *J Psychol* 22 67, 1946) assigns values to factors (blood sugar, skin temperature) during hyperventilation related to EEG The Cerebral Hyperventilation Index, C H I, is adjusted so that normals average plus and epileptics minus 120 persons (45 epileptics, 48 normals, 27 non epileptic patients) were individually given the Bell Adjustment Inventory for personality Excellent personality scores (35 persons) had average C H I of  $+4.5 \pm 0.59$  Average personality (58 persons) had C H I of  $+0.81 \pm 0.56$  Unsatisfactory personality (28 persons) had C H I of  $-0.89 \pm 0.83$  Aggressive personality (48 persons) had C H I of  $+3.4 \pm 0.37$  Average social score (50 persons) had C H I of  $+1.4 \pm 0.52$  and retiring personality had C H I of  $-3 \pm 1.3$  In epileptics excellent personality (8 patients) had C H I of  $+1.7 \pm 0.94$ , average personality (22 patients) had C H I of  $-2.5 \pm 1.3$  and unsatisfactory (14 patients) had C H I of  $-3.2 \pm 1.6$  In normals and non epileptic patients excellent personality (25 persons) had C H I of  $+5.6 \pm 0.5$ , average personality (41 persons) had C H I of  $+3 \pm 0.3$  and unsatisfactory (13 persons) had C H I of  $+2.3 \pm 1.3$  Good personality correlates with plus C H I (EEG with stands hyperventilation) The criticism of Ellis of the Bell Inventory (*Psychol Bull* 43 385, 1946) does not apply to physiological correlates

**On the role of acetylcholine and esterase during nerve activity** T C BARNES and R BEUTNER *Dept of Pharmacology, Hahnemann Medical College and Hospital of Philadelphia* The activity of true esterase can be demonstrated with mecholyl in the "oil cell" 0.0027 M mecholyl gave 47 mv negative at interface between saline and 5% cholesterol in guaiacol After shaking 5 hours (27°C) with 2 grams ground fresh rabbit brain per 100 c.c. the mecholyl solution gave a potential of 23 mv (100 mg % bicarbonate was present on both sides of the oil layer giving a pH of 8.2) In this experiment guaiacol did not come in contact with the esterase until the end of the test but we have recently found that esterase can be added directly to the oil cell 0.0027 M acetylcholine gave a potential of 30 mv in contact with 5% cholesterol in guaiacol (thermostat at 38°C) 1% human serum added to the oil cell reduced the potential to 5 mv negative in 2 hours of constant stirring Lyovac human plasma also contains active esterase 0.0027 M acetylcholine gives only 10 mv negative at a saline benzyl alcohol interface but this potential is slowly diminished when esterase is added to the oil cell According to Mendel, (personal com

munication) benzyl alcohol is not toxic to esterase. In living nerve anti-esterase drugs do not prolong the downstroke of the spike (Nachmansohn, *J Neurophysiol* 9 9, 1946), showing that esterase is not essential for impulse formation but probably has a minor but useful function removing excess acetylcholine.

**Oxygen dissociation curves of fetal and maternal sheep blood** D H BARRON *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn*. Oxygen dissociation curves prepared with fetal and maternal sheep blood, at several stages during the latter half of the gestation period of 150 days, demonstrate that curves for the fetal blood are markedly to the left of the maternal curves or ones prepared with blood from barren sheep. The fetal curves from the 80th day until birth tend to be hyperbolic in contrast to the sigmoidal maternal curves and to shift relatively little as gestation advances. The maternal curve shifts steadily to the right during this same period. At 80 days the pressure required to produce 60 per cent saturation in the maternal blood is 12 mm Hg greater than that to saturate fetal blood to the same degree, and about 20 mm Hg at 140 days. [*Aided by a grant from the James Hudson Brown Memorial Fund, Yale Univ School of Medicine*]

**The reduction of oxygen by hemoglobin compounds in acid and a method of polarographic analysis** J PERCI BAUMBERGER *Dept of Physiology, Stanford Univ*. The addition of acid to hemoglobin compounds results in the oxidation of the iron and the denaturation of the protein. Accompanying these changes, oxygen is used up in equivalent amounts depending on the type of hemoglobin compound reacting. Oxyhemoglobin and carboxyhemoglobin use up one half equivalent of oxygen and hemoglobin uses up one quarter equivalent while methemoglobin uses up no oxygen on addition to acid.

Some globin or ascorbic acid is oxidized when acid is added to oxyhemoglobin or carboxyhemoglobin but this is not the case with reduced hemoglobin or methemoglobin. This is due to the formation of hydrogen peroxide by oxyhemoglobin and carboxyhemoglobin but not by reduced hemoglobin on the addition of acid. The latter compound reduces oxygen to water instead of to hydrogen peroxide thus using up one half as much oxygen. Since oxyhemoglobin and carboxyhemoglobin act in an identical way, it must be that hydrogen peroxide is formed from oxygen not already bound to hemoglobin. It may be possible to show a relation between the degree to which oxygen is reduced in this reaction and the magnetic properties of the various hemoglobin compounds.

The analytical procedure depends on the polarographic measurement of the oxygen in acid before and after adding blood of different degrees

of saturation with air. Equations based on the different amounts of oxygen liberated and consumed permit the calculation of the relative concentrations of the various hemoglobin compounds present.

**Arterial temperatures in man** H C BAZETT, L LOVE (by invitation), E S MENDELSON (by invitation), and L H PETERSON (by invitation) *Dept of Physiology, Univ of Pennsylvania, Philadelphia, Pa*. Study of the heat exchange of the hand and foot indicates that precooling of arterial blood occurs during transit to the periphery, owing to the proximity of cooled blood returning in venae comites. Temperatures in the brachial and radial arteries have been measured by the use of needle thermocouples or of plastic covered couples introduced through a needle (diameter 0.4 mm). The temperature in the brachial artery has been measured 6 times in three subjects and the radial 13 times in five subjects. The temperatures have ranged in a neutral environment, brachial temperature from 37.1° to 36.3°, radial 36.5° to 35.5°, and in a cold environment brachial from 36.1° to 31.1° and radial from 33.0° to 21.5° C.

Plastic covered couples have been left in place for over two hours. Cooling of the hand causes an initial rise in the temperature of the brachial artery of about 1°, lasting 3 to 4 minutes and is followed by slow cooling. Rewarming of the previously cooled hand causes a precipitous fall in the brachial temperature. Light compression below the point of measurement causes a rise in temperature as the venous return along the artery is impeded. Drs R Day, R E Forster and J H Talbott cooperated in the initial experiments made at the Climatic Research Laboratory.

Support aiding different groups of experiments was given by O S R D, The Life Insurance Medical Research Fund, and a research contract for the Navy.

**Changes in arterial pH induced by compression and decompression** JOHN W BEAN *Univ of Michigan Medical School*. In order to determine what changes, if any, might occur in arterial blood pH as a result of compression and decompression, a glass electrode was placed in the circulating blood of anesthetized, heparinized dogs. Compression in air was carried to about 90 pounds in 3 or 4 minutes.

During compression there was a shift in the acid direction (0.15 to 0.02 pH), rapid decompression induced the reverse effect. The compressional shift is best explained as due to interference with CO<sub>2</sub> removal, since, (1) compressional inflow into the lungs can entirely prevent expiration, (2) the advancing front of inflow compresses the alveolar air, temporarily raising alveolar CO<sub>2</sub> tension and so obliterating or reversing the normal CO<sub>2</sub> diffusion gradient, arterial pH is therefore decreased. Cessa-

tion of compression permits resumption of expiration and a partial reversion of arterial pH in the alkaline direction. Decompressional outflow rapidly lowers alveolar tension and induces an alkaline shift in the arterial blood.

It would appear that the compression effects described above must of necessity be considered in any attempt to explain the reactions induced in man by rapid compression to high pressures, until these effects are proven to be inconsequential, the view that the reactions induced in man by compression are due solely to a suggested narcotic action of nitrogen is unwarranted. The decompressional pH changes hold important implications relative to explosive decompression, rapid ascent to high altitudes and rapid decompression from high pressures.

The arterial blood glucose level in alloxan diabetic dogs subjected to hemorrhage. *C. V. MESSER, II, B. VETTER* (introduced by Niguns I. Gregersen) *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* It has been shown previously (*Amer. Journ. Physiol.* 144: 233, 1945) that in dogs subjected to a standard fatal hemorrhage the blood sugar level rises to an average maximum of 111 mg. per cent above the control value.

The effect of the same standard fatal hemorrhage on blood sugar has been studied in a series of 11 dogs previously treated with enough alloxan to produce a blood sugar level above 200 mg. per cent. In this series the blood sugar rose 211 mgm. per cent (average) above the control level. However, the blood glucose concentration followed the same general pattern as in normal dogs, namely a rapid rise initially followed eventually by a sharp terminal decrease.

Measurements of the femoral arterial venous glucose differences in alloxan dogs subjected to hemorrhage reveal a rapid disappearance of blood glucose. Since Lackey et al. (*Proc. Soc. Exp. Biol. Med.* 57: 191, 1944) have shown that the liver glycogen is markedly decreased in alloxan diabetic animals, most of the glucose poured out of the liver after hemorrhage in these insulin deficient dogs presumably comes from gluconeogenesis. Considering the present disagreement as to the amount of gluconeogenesis in diabetes, it is interesting that these hemorrhaged diabetic animals showed such an ability to produce glucose.

Action of prostigmine methylsulphate on the reproductive organs of rats. *BETTY BAYLOCK* (by invitation) and *FREDERICK I. EMERY* *Dept. of Physiology and Pharmacology, Univ. of Arkansas*. The effect of prostigmine on the estrous cycle of rats was studied in a group of twenty mature virgin females. The series was divided into two groups of twenty animals each—Group A, controls, Group B, test animals—and estrous cycles were run daily

for a period of ninety days. Prostigmine was administered in daily dosages of 0.1 mg. in Group B during the second 30 day period. The number of animals in estrous and the length of the cycles were essentially normal in both groups for the first 30 day period. Following injections of prostigmine irregular cycles occurred, characterized by first a decrease in length, followed by a lengthening of the diestrous phase. After injections were stopped the cycles usually returned to normal within a few days.

After the ninety day period, both groups were sacrificed, and the uterus and ovaries removed and weighed. The weight of the uterus per 100 grams of body weight was found to be 204.5 and 264.1 milligram for the controls and injected groups respectively. The ovaries showed no significant change.

These observations on organ weights were further studied in mature virgin female rats, injected daily for a period of seven days with 0.1 mg. of prostigmine. On the eighth day the animals were sacrificed and again a significant change in weight was found in the uterus.

Studies were then made of mature male rats. A series of 12 animals each were injected for a seven day period with 0.1 mg. of prostigmine daily and then sacrificed. The testes were 26.0 per cent and the epididymides 7.0 per cent heavier than those of the untreated controls.

Enzymic formation of retinal vitamin A. *ALFRED F. BRISS* (introduced by David Rapport) *Dept. of Physiology, Tufts College Medical School, Boston*. Frog retinas contain a soluble protein which acts on the photoproducts of aqueous visual purple, forming large amounts of vitamin A. The factor is very labile at 25°C., losing nearly all its activity within 3 hours after the start of extraction. It is present in a large initial concentration, since the rate of vitamin A formation is maximal up to 2 hours after the start of extraction and then drops rapidly during the next hour. The rate is also strongly inhibited by acid or base, no activity being evident above pH 8 or after pretreatment of retinas in potassium aluminum sulfate. Acid solutions will react only when a fresh solution at about pH 6 is added. A cofactor can be washed from bleached and dried retinas by petroleum ether. The substrate of vitamin A formation is fairly stable for about 4 hours after bleaching at pH 4.2. During this time the initial photoproduct, the acid tautomer of indicator yellow, is replaced by retinene, without significantly changing the amount of vitamin A formed. Retinene is in turn converted to a colorless non-carotenoid which is incapable of forming vitamin A.

Suitability of the rat for routine laboratory work in physiology. *FRANK R. BLOOD* (by invitation) and *FRED E. D'AMOUR* *Univ. of Denver*

In many institutions the supply of dogs is insufficient to satisfy both research and instructional needs. The purpose of this paper is to demonstrate the feasibility of substituting rats for dogs in routine laboratory class-work, thereby releasing the latter for such research projects in which their use may be indispensable.

A course of 50 laboratory experiments has been designed, adequate for two quarters work in mammalian physiology, in which the only animal used is the rat. The distribution of experiments among the different organ systems is in fair accord with the emphasis usually given them, there being 6 experiments devoted to the blood, 12 to the heart and circulation, 6 to respiration, 7 to digestion and metabolism, 2 to excretion, 7 to the nervous system, 7 to the endocrine system and 1 to anaphylaxis.

In the presentation of this paper the scope of the course will be outlined, typical experiments from each group will be described, the few items of special equipment which the rat's size makes necessary will be illustrated and student's records and results given, to indicate how well the course works out in practice.

**Role of the kidney in resistance to ischemic compression shock** J. RICHARD R. BOBB (introduced by Harold D. Green) *Dept of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.* Renal compensation in shock has been postulated by Shorr, Zweifach and Furehgott (Science 102: 489-498, 1945). To test this hypothesis pairs of dogs were put into shock by compressing the hind legs with rubber tubes for six hours. In the hour prior to release of the tubes abdominal nephrectomy (ligation of the pedicle of the isolated kidney) was performed on one of the pair. On the control, a sham operation was done similar to the above except that the ligature was not tied around the pedicle. Test and control animals were kept side by side in a constant temperature room. Rectal and room temperatures were recorded by thermocouples.

Comparison of 11 test dogs with 11 control dogs gave no significant differences in the mean arterial pressures, survival times or rectal temperatures.

Three dogs, in shock produced as above and then nephrectomized, were crosstransfused (Green and Dennison, Rev. Sci. Instruments 16: 95-97, 1945) with three nephrectomized test dogs. As controls two pairs of nephrectomized, non-traumatized dogs were crosstransfused. Here again no differences could be discerned between the dogs crosstransfused with shock dogs and the controls in regard to mean arterial pressures, survival times or rectal temperatures.

It appears from these experiments that the kidney plays little part in the resistance of dogs to

this form of trauma [Aided by a grant from the Ella Sachs Plotz Foundation]

**Absence of any influence of heparin upon ischemic compression shock studied at various environmental temperatures**<sup>1</sup> J. R. R. BOBB (by invitation) and HAROLD D. GREEN *Dept of Physiol and Pharm, Bowman Gray Sch of Med of Wake Forest Coll, Winston-Salem, N. C.* Dogs which had been traumatized by 6 hours of ischemic compression of both hind legs developed during cross transfusion with test dogs more severe shock than did similarly traumatized dogs not crosstransfused (Green, Bergeron and Gustaphason, Fed. Proc. 4: 26, 1945). The present study was undertaken since the heparin used in the crosstransfusion studies might have contributed to the shock and since reports have appeared recommending the use of heparin therapeutically in other forms of trauma such as frostbite and incipient gangrene.

Dogs anesthetized and traumatized as above were studied in pairs. One of each pair received 25 mg/kg of heparin<sup>2</sup> one hour before release of the compression and 0.5 mg/kg at half-hour intervals thereafter for 9 injections. This amount of heparin prevents clotting in vitro for approximately 24 hours. Rectal, room and intramuscular temperatures were recorded continuously by thermocouples.

Six dogs kept at an environmental temperature above 30°C died within 6 hours. Sixteen studied at lower temperatures survived longer but none survived indefinitely. Between the two dogs of each pair no differences were observed in rectal temperature, leg temperature, survival time or autopsy findings.

It is concluded that heparin neither favors nor prejudices the behavior of animals subjected to this form of trauma and that the increased severity of the shock in the earlier studies was due to the crosstransfusion procedure.

**Riboflavin and other fluorescent compounds in a developing egg** J. H. BODINE and LAURENCE FITZGERALD (by invitation) *Zoology Lab, State Univ of Iowa.* A quantitative study has been made of the riboflavin and other fluorescent compounds in the egg of the grasshopper (*Melanoplus differentialis*) throughout its entire development. The average amount of riboflavin in the egg of the grasshopper is 15-17 gammas per gram wet weight. Total fluorescence of the egg at pH 4.5 remains practically constant throughout development. The egg, when laid, contains riboflavin and a non-reducible, non-diffusible fraction fluorescing at pH 4.5. This fraction makes up approximately 1/3 of the total fluorescence of the egg at pH 4.5.

<sup>1</sup> Aided by grant number 576 from the Council on Pharm and Chem of the Am Med Assoc.

<sup>2</sup> The heparin was supplied through the courtesy of Lederle Laboratories, Pearl River, N. Y.



A non-reducible, non-diffusible fraction fluorescing at pH 10 is also present in the egg when laid. This fraction makes up less than  $\frac{1}{3}$  of the total fluorescence of the egg at pH 10. Riboflavin, as such, remains constant in amount until late in the development (post diapause) of the embryo. Late in development there is produced fluorescent compounds which are diffusible and fluoresce in both acid (pH 4.5) and alkaline media (pH 10). In acid medium (pH 4.5) they are reducible. These compounds produced late in the development of the egg are thought to resemble pterines. A marked economy in the use of riboflavin by the egg during its development is pointed out. No free riboflavin is found in the nymph when hatched.

Urea synthesis in the adrenalectomized-nephrectomized rat on low potassium diet. PHILIP K. BONDY and FRANK L. DUCHI (introduced by FLEET A. STAN, Jr.) *Dept. of Medicine, Emory Univ. School of Medicine, Atlanta, Georgia*. The rate of urea synthesis was studied in normal and adrenalectomized male rats after nephrectomy. Adrenalectomized nephrectomized rats on the usual chow diet survived less than 24 hours, however, if prepared by a low potassium high sodium diet for three days prior to operation, their average survival time was  $98.4 \pm 5.2$  hours. Nephrectomized rats with intact adrenals similarly prepared survived  $77.1 \pm 5.6$  hours. Blood urea levels were determined at intervals until death and the rate of urea formation per hundred grams body weight per hour calculated on the assumption that urea is equally distributed throughout the body water, i.e. 75 per cent of body weight. The rate of rise of urea in adrenalectomized rats remained constant from nephrectomy to death and was significantly diminished as compared to normals in which the rate increased progressively until death. The effect of adrenalectomy was noted within 16 hours after adrenalectomy. The terminal urea levels of the normal rats were significantly higher than those of the adrenalectomized animals. In a third series of adrenalectomized nephrectomized rats prepared on low potassium diet, subcutaneous administration of 1 ml of Upjohn's aqueous Adrenal Cortical Extract twice daily caused a rate of urea formation intermediate between adrenalectomized and non-adrenalectomized rats. The unchanging rate of urea formation in the adrenalectomized rat probably reflects the inability of the rat lacking cortical function to respond to the continuing stress of nephrectomy and the consequent uremia and acidosis.

Similar studies are in progress with regard to the rate of deamination of parenterally administered amino acid preparations in adrenalectomized nephrectomized and normal nephrectomized animals. [Aided by a grant from the Committee on

Research in Endocrinology, National Research Council.]

The time relations of the electric response of cardiac muscle. JOHN BOZLIN *Dept. of Physiology, The Ohio State Univ., Columbus*. An attempt was made to determine the time relations of the monophasic potential from differential potentials according to Hill's method. The requirements for the validity of this method (distance of leads of less than 5 mm, uniformity of tissue between leads) can be met only incompletely. Using non-polarizable tubular electrodes, of very small size, the potentials from the surface of the dog's and cat's heart were rather variable, but the largest and at the same time simplest of these showed an R-wave lasting only 1 to 2 msec., a brief S wave and a small T wave. The monophasic potential derived from the differential potential shows a rise to the maximum 2 msec. or less, a brief spike and following plateau like the monophasic potentials recorded in the usual manner. The RR interval was the same for all parts of the ventral surface of the heart.

Renal extraction of p-aminohippurate in normal subjects and in essential hypertension and chronic diffuse glomerulonephritis. STANLEY E. BRADLEY, JOHN J. CURRY, and GERALDINE P. BRADLEY (introduced by Hans O. Haterius) *Dept. of Medicine, Boston Univ. School of Medicine and the Liens Memorial, Massachusetts Memorial Hospitals, Boston, Massachusetts*. The renal extraction of sodium p-aminohippurate (PAH) has been determined in 22 normal human subjects, in 10 patients with essential hypertension and in 6 patients with chronic diffuse glomerulonephritis. The extraction of PAH was calculated from the difference between its concentration in the right renal venous blood, obtained by venous catheterization, and the peripheral blood. PAH clearance and Tm, and mannitol clearance, were also determined in the subjects with renal disease. All subjects were examined under basal conditions.

In the normal subjects, PAH extraction ranged from 87.5 per cent to 100.0 per cent, averaging 92.5 per cent. When blood was sampled from the left renal vein this value was much less, presumably because of the admixture of blood from the left ovarian or spermatic veins.

In essential hypertension, PAH extraction ranged from 85.4 per cent to 95.6 per cent whereas the values for its Tm varied between 28.2 mgm. per minute to 103.3 mgm. per minute. In subjects with chronic diffuse glomerulonephritis, a wider range and lower values of PAH extraction were found (58.1 per cent to 76.4 per cent) although a similar range of PAH Tm (21.6 mgm. per minute to 80.9 mgm. per minute) was observed.

Perfusion of non-functioning tissue or the operation of arterio-venous shunts may account for the



depression of PAH extraction found in glomerulonephritis. In essential hypertension, on the other hand, PAH extraction tends to remain within normal limits, presumably because any kidney damage in this disease is secondary to occlusive vascular disease (arteriosclerosis) which prevents perfusion of non functioning tissue.

**Renal oxygen consumption and sodium p-aminohippurate (PAH) extraction in normal man during abdominal compression** STANLEY E. BRADLEY and MEYER H. HALPERIN (introduced by Hans O. Haterius) *Dept of Medicine, Boston Univ School of Medicine and the Evans Memorial, Massachusetts Memorial Hospitals, Boston, Mass.* Effective renal plasma flow, measured in man by the PAH or diodrast clearance, is sharply reduced by abdominal compression at 80 mm Hg. Further studies have been made to determine if this apparent alteration in plasma flow might arise from impaired extraction of PAH or diodrast. In addition, renal oxygen consumption has been measured before, during and following the application of abdominal compression in normal human subjects.

Renal blood flow was measured in five normal subjects by the PAH clearance corrected for the arterial hematocrit and renal PAH extraction. PAH and oxygen content were determined in samples of renal venous blood, obtained by the catheterization technique, and peripheral arterial blood collected simultaneously. The values for venous oxygen content were corrected to the hematocrit of the corresponding arterial samples to avoid errors attributable to dilution during sampling or during the passage of blood through the kidney. All figures were corrected to ideal body surface (1.73 M<sup>2</sup>).

Renal extraction of PAH was not altered significantly by the application to the abdomen of a pneumatic girdle inflated to a pressure of 80 mm Hg. Renal blood flow fell on every occasion, on the average from 1102 cc per min to 556 cc per min, returning to 1275 cc per min following release of pressure.

Renal oxygen consumption varied between 6.92 cc per min and 16.75 cc per min. The oxygen extraction (arterio-venous difference) did not change significantly during compression except on one occasion when it rose. In this instance, the renal venous oxygen content fell markedly, but in the remainder, as well as in seven additional subjects in whom only renal venous oxygen contents were determined, this value rose or remained relatively unchanged. Omitting this subject, renal oxygen consumption fell on the average from 14.02 cc per min to 5.93 cc per min during compression and returned to 14.76 cc per min after release.

**The effects of diisopropyl-fluorophosphate upon the submaxillary gland** CHARLES R. BRASSFIELD, LOUIE BICINS (by invitation), and MERIE M.

MUSSELMAN (by invitation) *Physiology Lab., Univ of Michigan, Ann Arbor, Michigan.* The effects of diisopropylfluorophosphate (DFP) on the submaxillary gland of dogs were studied by injecting the drug into the isolated arterial supply of the gland. Two types of response were noted. In some animals each injection of DFP (3 mg in one half cc saline) induced a quick response lasting about one to two minutes and producing from one-half to one cc of saliva. As the injections were continued, the primary stimulation decreased but the gland began to secrete continuously. This continuous secretion speeded up with each injection until a maximum rate was established. In the second type of response, which was more common, no effect was noted until after the second or third injection. Then a slow continuous secretion would begin. With each additional injection the latent period would shorten and the rate of flow would increase until the maximum rate of flow was established. After the maximum continuous rate of flow was developed, further injections of DFP would slow the rate and eventually stop it completely. The effects upon the maximum secretion rate of CO<sub>2</sub> administration or ammonium chloride injection were studied. No change or a slowing was obtained by these procedures. However, if the gland had not been completely poisoned these procedures frequently caused an increase in the rate of secretion. A study of the blood flow often indicated an inverse relation between blood flow and secretion when the gland was completely poisoned.

**Retention of sex functions after isolation of pars anterior by extirpation of the hypophyseal stalk** C. G. BRECKENRIDGE (introduced by A. D. Keller) *Dept of Physiology and Pharmacology, Baylor Univ College of Medicine, Houston, Texas.* The distal portion of the pars anterior was isolated by the surgical procedure of removing the hypophyseal stalk tissue and the proximal portion of the pars anterior in nine dogs. The differential staining procedures of Mallory azan, Rasmussen's copper chrome hematoxylin, and Hansen's chromalum hematoxylin were utilized to demonstrate aberrations in the chromophilic cells as well as alterations in their populations.

Sexual functions remained completely intact in two dogs as evidenced by their ability to reproduce. As judged by gross and histological studies, the ovaries and genital tracts remained normal in four other females of the group. In the three remaining dogs the ovaries and genital tracts as revealed by histological studies were markedly atrophied.

There was no correlation between retention of sex functions and the size of the isolated mass of the pars anterior tissue which remained following the surgical procedure. Two of the dogs, in

which there was obvious sex regression, had as much and in one instance more, viable pars anterior tissue than did the dogs which retained sex functions

There was a definite correlation between retention of sex functions and the cytology of the pars anterior remnant. Those animals in which normal functions persisted were shown to possess numerous well granulated acidophile and basophile cells, while those in which regression occurred gave evidence of decreased numbers of chromophilic cells as well as a paucity of granules in those which remained viable [ *aided by a grant from the John and Mary R. Markle Foundation* ]

Intracellular granules in the hypothalamus and infundibulum of the dog C. G. BRECKENRIDGE (introduced by A. D. Keller) Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine, Houston, Texas. The hypothalamus and pars nervosa was studied in a series of normal adult dogs to determine the presence and distribution of cells containing intracellular granules of the type ordinarily correlated with secretory function. Distinctive granulations were observed following the application of the Mallory azan method and in some instances granules as well as a lipid substance were differentially stained within the same cell. Although adjacent sections were stained with cresyl violet and copper chrome hematoxylin only the latter revealed the presence of intracellular granules.

Both the anterior and posterior divisions of the supraoptic nucleus (nucleus tangerialis of Rioch) contain cells which are tentatively divisible into three categories. The first cell type possesses a large nucleolus and cytoplasm bearing carminophilic granules which are large, discrete, and spherical. They are also located in some of the cell processes which project downward toward the floor of the hypothalamus. The second, more numerous, cell type is characterized by having a cytoplasm filled with many small, spherical, basophilic granules. The third type conforms to the usual neuronal cell.

Some of the cells in the infundibulum contain carminophilic granules while others are basophilic in their staining reaction. These cells are more numerous in the proximal portion of the stalk, while distally they decrease in numbers to disappear in the junctional region with the infundibular process.

Some of the cells in the paraventricular nucleus and in one tuberal nucleus contain carminophilic granules of a character similar to those observed in the supraoptic nucleus [ *aided by a grant from the John and Mary R. Markle Foundation* ]

Immediate and permanent dwarfing with subsequent sexual development following near-ordinary hypophysectomy in three-months-old female

puppy C. G. BRECKENRIDGE (by invitation) and A. D. KELLER Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine, Houston, Texas. A female pup, which was whelped by a large hound and sired by a large shepherd, was hypophysectomized (near ordinary attempted) when three months old. The pup immediately stopped growing and remained permanently dwarfed, except that the genital tract grew and developed normally, ultimately attaining the full size and characteristics of an adult large dog. At operation, the pup weighed  $5\frac{1}{2}$  kg, and when the experiment was terminated 20 months later, it weighed 5 kg, whereas a male litter mate attained a weight of 11 kg. The over all length of the dwarf's genital tract measured 11 inches, while that of a litter mate pup at  $3\frac{1}{2}$  months of age measured  $4\frac{1}{2}$  inches. Accordingly, dwarfing of the genital tract did not occur.

The dwarf exhibited three normally spaced estrus periods subsequent to sexual maturity, but she was not mated. Microscopic examination of the ovaries revealed numerous primordial ova, follicles in various stages of development, and three ruptured follicles with early corpus luteum formation.

Histologically, the major portion of the pars tuberalis and only a very small remnant of pars anterior tissue remained viable. The pars anterior remnant was essentially devoid of acidophiles, but the basophiles were well represented. Basophiles meeting the cytological criteria for those found in the pars anterior were also present in the tissue which is ordinarily considered as the "compact portion" of the pars tuberalis [ *aided by a grant from the John and Mary R. Markle Foundation* ]

Relation of optimum frequency for A. C. excitation to impulse frequency in chemically excited axons. FRANK BRINK Johnson Foundation, Univ. of Pennsylvania. Analysis of the temporal distribution of impulses in calcium deficient nerve fibers shows the fundamental frequency of the excitatory process to be a characteristic of each fiber (Annals of New York Academy of Sciences 47: 375, 1946). The relation of this frequency to the optimum frequency for excitation by alternating current has been investigated.

Single A fibers in excised frog sciatic nerves were mounted on electrodes and the amplified action potentials observed or recorded. The fiber was stimulated through electrodes (chlorided silver or calomel) connected to the nerve trunk. Threshold intensity of applied potential at each frequency was determined by slowly increasing the amplitude from zero. Subsequently, diffusible calcium chloride was progressively removed from the nerve. The threshold measurements were repeated at intervals. Finally, the repetitive activity characteristic of calcium deficiency occurred

The frequency of the excitatory process was estimated from records of this activity. In similar measurements on five giant axons of Squid (*Loligo pealii*) both the recording and stimulating electrodes were connected to the isolated axon.

In frog fibers the optimum frequency for A-C excitation is lower than the fundamental frequency of repetitive response caused by calcium deficiency. The lowering of thresholds contingent upon calcium removal does not change this relation. Ultimately the low frequency thresholds are affected more than those above the optimum and the A-C excitation curve becomes asymmetrical. However, in the giant axon of Squid a definite optimum frequency for electrical excitation is developed in calcium-deficient nerves which coincides with the frequency of chemically initiated impulses.

**Comparative effects of positive and negative accelerations** S W BRITTON and V A PERTZOFF (by invitation) *Univ of Virginia*. Experiments have been carried out to determine the effects on carotid and femoral arterial pressures, taken simultaneously, of positive and negative acceleratory forces on dogs and monkeys. Blood flow was also investigated. Well over 700 experimental runs were made.

Arterial pressure changes occur more quickly in that part of the animal towards the periphery of the centrifuge, whether positive or negative g forces be considered. That is, in the case of positive g the pressure change appears earlier in the femoral artery, while in negative g tests it occurs earlier in the carotid vessel.

A reciprocal relationship between heart rate and arterial pressure is apparent only in the case of reduced supply (flow, pressure) to the head. The involved reflexes were studied.

A distinct physiological advantage is possessed by the monkey over the dog (or cat) subjected to acceleratory forces. This advantage is shown in both carotid and femoral pressure values, and approximates 1 g in the different tests used. A higher degree of vascular accommodation to gravity appears to have been developed in the case of the anthropoid type.

Investigations indicate that the overall effects produced on the organism by acceleratory forces should be considered on the basis of the product  $t \times g$  [Work carried out under a contract between U S Navy, Office of Naval Research, and the Univ of Virginia].

**Regulation of energy exchange in rats** J R BROBICK *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn*. It is now possible to outline the nature of regulation of physiological energy exchange in rats from data obtained in experiments designed to control, to measure, and arbitrarily to change all four of the variable factors involved, namely, energy storage (body weight),

work output (spontaneous locomotor activity), heat loss and energy intake as food.

Other factors remaining constant, body weight increases with increased food intake, decreases with increased activity, and decreases with increased heat loss. Activity increases with decreased food intake, and increases with increased heat loss resulting from exposure to cold. Heat loss temporarily increases with increased activity and increases with increased food intake. Food intake increases with increased heat loss during cold exposure, while during exposure to heat, food intake may be depressed far enough below energy expenditure to bring about a large energy deficit. Food intake also appears to be temporarily depressed with increased activity.

Some of these results appear to be paradoxical if the mechanisms of regulation are assumed to be capable of maintaining an exact balance between energy intake and output under all conditions. No paradox appears, however, if activity and food are considered to be first of all potential sources of heat for the animal, and if the basis of regulation of physiological energy exchange is assumed to be the effect which each of the four variable factors has upon body temperature regulation. [Aided by grants from The Fluid Research Fund and The George H Knight Memorial Fund, Yale Univ School of Medicine].

**Some physical factors in receptive relaxation**<sup>1</sup> DANIEL A BRODY (by invitation) and J P QUIGLEY *Division of Physiology and Pharmacology, Univ of Tennessee, Memphis, Tennessee*. The ability of hollow viscera to receive quantities of material without a significant rise in intra-lumen pressure ("receptive relaxation") was investigated by (a) consideration of the physical factors involved and (b) an analysis of pressure/filling curves from spherical rubber balloons (artificial elastic viscera).

These curves showed 4 successive phases: (1) a precipitous rise beginning with the initial stretching, (2) a rapid fall, (3) a slower fall, and (4) a gradual rise. Except in the range of distentions where rubber failed to follow Hooke's law, the actual values approximated those predicted.

Predicted values are based on the following expression:  $P = k \frac{r - r_0}{l^n}$  ( $P$  = intralumen pressure,  $k$  = constant,  $r$  = radius,  $r_0$  = radius at onset of wall stretching,  $n$  = integer). We have arrived at values  $n = 2$  and  $k = 4E d_0$ , where  $E$  = Young's modulus and  $d_0$  = the unstretched thickness.

"Receptive relaxation" is not entirely dependent on neuromuscular mechanisms, for this phenome-

<sup>1</sup> This investigation was supported by U S P H Research Grant #101.

non is exhibited by portions of the pressure/filling curve of the *artificial viscus* derived either theoretically or experimentally. For example, eight-fold volume distention of a spherical viscus, final intralumen pressure equalling the original, necessitates doubling the wall tension and increasing the wall "tone" four fold.

Additional developments of this character permit calculation of the wall tension and "tone" of a spherical viscus, if the intralumen pressure and size are known and may be extended to include similar calculations in cylindrical, ellipsoidal and certain irregular hollow viscera.

The inhibition of inorganic phosphate liberation in the presence of hexokinase activity. R. H. BRON KAHN (by invitation) and I. ANTON VINSKY, *May Inst. for Medical Research of the Jewish Hospital, Cincinnati, Ohio*. Aqueous extracts of rat muscle show an increase in their inorganic phosphate content during aerobic incubation. This increase is abolished by the addition of both glucose and ATP but not by either alone.

Since these extracts display hexokinase activity (i.e., transfer of labile phosphorous from ATP to glucose to form glucose 6 phosphate) there appears to be a relationship between hexokinase activity and the above mentioned increase in inorganic phosphate. Under all conditions investigated, the presence of hexokinase activity was associated with the absence of this increase and, conversely, the absence of hexokinase activity was associated with an increase in inorganic phosphate. Even with the addition of ATP and glucose, this increase in  $P_o$  was observed in the presence of various hexokinase inhibitors. The above described phenomena were observed in fluoride poisoned systems.

Whereas the mechanism involved and the significance of this observation have not been further investigated, it would appear possible that hexokinase activity presents a means by which the non-glycolytic conversion of high energy phosphorous compounds to low energy phosphorous compounds may be inhibited.

Relation of areas of cortical ablation to the leg responding to a conditioned stimulus. REG. B. BROMLEY (introduced by Philip Bird), *Dept. of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore 5, Md.* Unilaterally decorticate cats, trained in a shock avoidance conditioned response situation with the unconditioned stimulus applied to the leg contralateral to the ablation, tend to give conditioned responses of the unshocked leg. When trained with the shock applied contralateral to the intact hemisphere, the responses are of the shocked leg as is the case with normal cats trained by the same technique.

Preparations with one frontal pole ablated behave as do the hemidecorticates, those with one

occipital pole ablated, however, give normal responses. Some animals with somatic sensory area I or II removed on one side responded like normal animals. Others with these ablations gave a number of conditioned responses of the unshocked leg, but not to the extent shown by hemidecorticate or frontal pole preparations and, in the course of training, they finally responded with the shocked leg only.

A conditioned response of either of the pair of legs being studied (fore or hindlegs) resulted in avoidance of the shock. The conditioned stimulus was auditory. The effect of removal of auditory areas is being studied.

Conditioned responses in a decorticate dog. REG. B. BROMLEY (introduced by Philip Bird), *Dept. of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore 5, Md.* The literature contains several reports of the development of a conditioned response in a decorticate animal, but doubt exists as to the specificity of the response. This report is based on one decorticate dog which survived 33 months and was studied in a shock avoidance conditioned response situation. The preparation learned to give discrete conditioned responses (lifts of a hindpaw) to an auditory stimulus. Following 100 trials of overlearning and 43 days without training, the dog was retrained in 200 trials to a criterion which previously had required 700 trials. Later the conditioned response to the auditory stimulus was experimentally extinguished, and concurrently one to a visual stimulus established, the animal made this discrimination in 165 trials.

The animal was very easily disturbed and exhibited maximum sham rage. If he became disturbed in the conditioning apparatus, training was terminated for the day. As a rule when a shock, of sufficient intensity to produce a flexion, was applied to one leg, sham rage did not appear. If, however, both hindlegs or a foreleg and a hindleg were shocked it invariably appeared.

Histological examination indicates that practically all neocortex had been removed bilaterally, only minute fragments of the cortex of gyrencephalus, of the insula and of the limbic fields being detectable. On both sides the putamen is severely damaged, the caudatus and amygdala are almost intact.

The time course of recovery oxygen consumption in nerve. D. W. BRONK, F. BRINK, C. M. CONNELLY (by invitation), F. D. CARLSON (by invitation), and P. W. DAVIES (by invitation), *Johnson Foundation, Univ. of Pennsylvania*. By means of the oxygen electrode, which we have previously described, we have determined the rate of oxygen consumption of nerve during a period of stimulation and at brief intervals during the course of recovery. It is thus possible to relate

the time course of oxygen consumption to the rate of recovery heat production previously measured by Hill and his associates

An oxygen electrode is mounted in a chamber containing frog or crab nerve and into this chamber Ringer's fluid containing oxygen at a known tension flows at a constant rate. When an appropriate difference of potential is maintained across the electrode immersed in the out-flowing fluid, the electrode current is a direct measure of the rate of oxygen consumption of the nerve.

Experiments which have been made thus far indicate that in crab nerve the oxygen consumption following activity does not last as long as the reported recovery heat production, although in frog nerve an extra oxygen consumption has been observed for as long as 30 minutes following prolonged stimulation. In both frog and crab nerve there is a lack of parallelism between the time course of oxygen consumption and heat production. In order to determine the significance of these relationships the effects of frequency and duration of stimulation and of temperature have been investigated. Also, the effects of veratrine, yohimbine and azide on the time course of oxygen consumption will be discussed in relation to after potentials and the metabolic processes.

The relative effectiveness of fructose and glucose in the alleviation of insulin shock. JOHN R. BROWN (by invitation), ANDREW A. ORMSBY (by invitation), BYRON M. HENDRIX, and D. BAILEY CALVIN. *Laby of Biological Chemistry, Univ of Texas, Medical Branch, Galveston*. Female dogs were used in the experiments being reported. Preliminary experiments were carried through to determine insulin dosage necessary to produce a hypoglycemic shock-like condition. Following this, the relative effectiveness of glucose and fructose given intracardially in the alleviation of the hypoglycemic condition was followed.

Determinations of total blood and urinary sugar and fructose were carried through in most experiments, and careful attention was given to physical symptoms involving muscular weakness as an additive determinant of relief from shock. Generally speaking, the best criterion of shock was found to be a completely atonic state, which occurred when the blood sugar levels fell to approximately 20 to 25 mgm per cent. These experiments showed that fructose, given in the same amount per unit of body weight, was not as effective as glucose either in immediate or prolonged relief of the hypoglycemic shock condition. Although some indication of immediate relief was observed, nevertheless dogs to which fructose had been administered relapsed more quickly than was the case for dogs in which glucose had been used.

Generally speaking, where equal doses of glucose or fructose were given, the loss of sugar in the

urine was found to be approximately the same within fairly narrow limits.

The data reported indicate that intracardial fructose is not as rapidly available to the animal organism in insulin shock as is the case for glucose, and that fructose will not sustain the animal following the initial slight recovery phase [Supported by a grant from the Sugar Research Foundation].

The effects of pilocarpine hydrochloride on hepatic bile secretion. ROBERT V. BROWN. *Dept of Pharmacology, Univ of Tenn Med School, Memphis, Tenn and Univ of North Dakota*. An attempt to determine the effects of pilocarpine HCl on hepatic bile flow was made by clamping the cystic duct, cannulating the common bile duct and recording the rate of secretion. Using sodium pentobarbital, 32 mg per kg, supplemented by ether as necessary, results were equivocal. Although the rate of secretion was markedly changed, over a period of ninety minutes no constantly reproducible results were obtained in twelve dogs.

Using sodium barbital, 250-300 mg per kg, as the anesthetic, present incomplete data indicate some stimulation of secretion by pilocarpine. There is increased bile flow for a few seconds after the drug injection, possibly from contraction of the duct system, following this is a period lasting about fifteen minutes during which there is little or no secretion. The rate of secretion is then markedly increased for many (15-30) minutes. In some animals, the total secretion for the experimental period of ninety minutes is equal to or less than that of the control period of secretion, in other animals the total secretion over the ninety minutes is significantly greater than that of the controls. Further experiments are in progress to attempt to determine the factors responsible for the variability of the results [Partially supported by the Committee on Therapeutic Research of the American Medical Association].

Changes in visual functions and performance after 2 hours of intensive inspection work at 2 footcandles. JOSEF BROZEK (by invitation), ERNST SIMONSON, and ANCEL KEYS. *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis*. The work task reproduced the essential features of an industrial conveyor inspection-operation. It involved recognition of irregularly spaced letters (visual angle about 1 minute) passing through a narrow slit in front of the subject. Performance was evaluated on the basis of 6 minute work samples of 200 letters. The score was expressed as the number of letters correctly copied.

Six normal young men served as subjects. The mean performance score decreased from 162.0 at the start to 137.2 and to 136.0 after one and two hours of strenuous visual work. These changes were statistically significant (with 1 and 5 degrees

of freedom the  $t$  value for the significance of the mean decrements was 8.23\* and 18.29\*\*, respectively.)

Visual functions were studied before and after work. The results will be given as means (M) before the start of the work, difference (d) indicating deterioration (-) or improvement (+), and the  $t$  test of the mean change. Decrease in fusion frequency approached significance (M 15.7 flashes per second, d -0.9 1.6 32). Changes in blinking rate and in recognition time of the location of dots (threshold size) were not statistically significant.

Voluntary eye movements were studied with the ophthalmograph. The overall speed was lowered (M 4.20 movement fixation cycles per second, d -0.82 1.8 89\*) due primarily to the lengthening of the fixation phase of the cycle (M 0.191 sec, d -0.038, 1.23 87\*\*). The movement phase did not change significantly (M 0.072 sec, d -0.006 1.4 15). Precision in fixating the targets deteriorated (M 2.32 units, d -1.13, 1.11 51\*). [This work was supported by a grant from the Lord & Ray Corporation Toledo Ohio.]

The concentration of protein in normal urine measured by its surface activity. ALAN C. BENTON and R. GUSTON (by invitation) *Medical School Univ. of Western Ontario*. Very small concentrations of proteins can be measured by the area of a monofilm formed when the fluid containing them is dropped slowly on a suitable buffer (method of Gorter and Grendel). The method has been developed for a rapid estimation of protein in very small samples of urine. Non protein, but surface active substances are present in normal urine but their activity is relatively constant and insignificant in the total activity, where there is albuminuria of clinical significance. The 'residual' or non protein activity is eliminated if the total activity is measured before and after precipitation by a specific protein precipitant (Tsu-chiwa's Reagent).

In samples from 100 normal male subjects the mean concentration of protein was found to be 3.7 mgs % with a mode of less than 2 mgs %. Less than 5% had concentrations greater than 12 mgs % protein. A prediction curve has been constructed by which the probability that a given sample of urine is "normal" can be determined.

Since the normal range runs out at 12 mgs % while the usual clinical tests give indications described as "insignificant" if the concentration is less than 50 mgs %, the usual tests have inadequate sensitivity. In a group of 40 patients with labile hypertension, 40% of these showing pre-tensionuria by clinical tests had concentrations of protein significantly greater than the normal range.

Further observations on epithelial movements in wound healing. WILHELM BUSCHKE (introduced by Selig Hecht) *Wilmer Ophthalmological Inst.*,

*Johns Hopkins Univ., Baltimore, Md.* It has previously been reported that the healing of small (30 micra diameter) pin prick injuries of rats' corneal epithelium starts by a radial orientation of the surrounding epithelium after a lag period of one hour, and proceeds by a movement of the epithelium into the defect which—at body temperature—is covered with a complete cell layer within 3 hours; these epithelial movements are—in part reversibly—inhibited by various agents, notably the local anesthetics, low temperature ( $Q_{10} = 5$ ), anoxia, and several metabolic poisons which are known as inhibitors of oxidative pathways (Friedenwald and Buschke, *Jl Cell & Comp. Physiol.* 23, 95, 1911, *Arch. Ophth.* 32, 110, 1911).

Recent experiments have shown that quinones and naphtha quinones are among the strongest inhibitors of these movements, with threshold concentrations of M/5000 to M/1000. Iodoacetate also inhibits in similar concentrations. Various mercurials and trivalent arsenicals also inhibit in concentrations of M/1000 to M/500. These experiments suggest that sulfhydryl groups play an essential role in these woundhealing movements. Both quinones and metallic compounds as well as iodoacetate in similar or slightly higher concentrations cause a loosening of the epithelium from the stroma after incubation, in contrast to the effect of these agents, the inhibition of cell movements caused by lowering of the temperature and by anoxia is not accompanied by loosening of the epithelium.

The radial arrangement of the cells surrounding small pin pricks and also at the ends of linear lesions is not seen along the extension of linear lesions or along the circumference of larger lesions in early stages of healing, in the beginning healing of these lesions, the immediately adjoining cells become tangentially oriented, and only the more distant epithelium orient radially towards the lesion. It is suggested that in some phases of the healing process the syncytial nature of the corneal epithelium is of importance and that forces play a role which act on it as on a surface coat. [Supported in part by a grant from the John and Mary R. Markle Foundation.]

The electroarchitectonic map of the antidromic potential. BENNY CAMPBELL *Univ. of Minnesota Medical School*. The potential record from the spinal cord taken with single fine probe electrodes varies, during the antidromic firing with the position of the recording tip relative to the structures within the cord. From the dorsal surface as well as from the dorsal columns and the entire contralateral side, the time of the arrival of the volley in the motor nucleus is marked by negativity, the amplitude varying with the distance from the motor neurons. Strongly triphasic records are

obtained in the ventral white column in the path of the emergent axons. From the motor nucleus itself, a long lasting positivity, with no trace of the negative deflection is seen.

Using the cartographic technique previously described by the author for mapping the isopotential contours within the spinal cord, maps illustrating the location and the time distribution of the potential fields from the first deviation to 3.0 msec after arrival of an antidromic volley have been prepared. The position of the nucleus fired (tibial) was determined by degeneration and each electrode placement checked histologically. The locus of the cells is characterized by an immediate and long-lasting positivity. No field of negativity is encountered in the region of the cell bodies. Medially, however, in the intermediate gray matter, a shorter lived negative field develops. This is continuous to the dorsum of the cord and accounts for negative deflection of the surface potential. Erroneous interpretations which have entered the literature because of neglect of histological control are explainable on the basis of the steepness of the potential gradients.

**Stratification of bile in the gall-bladder and its relation to cholelithiasis.** B. A. CAMPBELL (by invitation), ALAN C. BURTON, P. FITZJAMES (by invitation), and A. BERNSTEIN (by invitation). *Medical School, Univ of Western Ontario*. Radiological evidence (Bernstein) suggests that the bile in the gall bladder of patients with cholecystitis and normal subjects is not uniform but layered in distinct strata of different composition. Independent evidence of stratification has been obtained in freshly excised gall-bladders of cattle, by measuring specific gravity, colour index, concentration of bile salts and cholesterol, and pH in samples withdrawn at different levels.

Marked differences in specific gravity and other variables exist from top to bottom in many cases, and persist many days in spite of diffusion or manipulation of the gall-bladders. Often changes are abrupt and suggest sharp "interfaces" between different biles.

Samples taken at different levels have also been obtained in patients during and after operation (cholecystectomy), which show stratification, and stones which float at the interface between layers. It is concluded that stratification of bile occurs physiologically in the gall-bladder.

Precipitation of cholesterol occurs at the interface when bile is layered with distilled water, and can be explained on the basis of a slower diffusion of cholesterol than of bile salts between layers. It is suggested that persistence of stratification, due to incomplete or absent contractions of the gall bladder, may be an important factor in the formation of cholesterol stones.

**A method suitable for application of moist**

**heat therapy and applicable for controlling moist chambers.** L. D. CARLSON and H. L. BURNS (by invitation). *Dept of Physiology and Biophysics, Univ of Washington, School of Medicine, Seattle, Washington*. Black, neoprene rubber sponge holds a large quantity of water, is heat resistant, and absorbs infra-red light. Sealing the sponge rubber on five sides allows water vapor to escape in one direction. Preliminary experiments have demonstrated that an infra-red lamp, acting on a  $\frac{3}{4}$ " sponge rubber pad, provides temperatures of 38° C in five minutes and 65° C in 15 to 20 minutes. Moisture loss under the most severe conditions was approximately 10% in one hour. The limiting factor in these experiments was the type of infra-red lamp available. The use of GE 250T10/1 or T10 lamps materially improves the performance and design. A Fenwal Midget Thermoswitch or Fenwal Cart ridge Thermoswitch, A7000, can be used to control temperature. Use of this method may eliminate tedious towel wringing techniques, provide a means of having moist heat at a constant, known temperature, and provide a method of quantitative study of the variable factors in moist heat therapy. The design also has value for laboratory, controlled temperature and humidity studies involving small chambers.

**Oxygen requirements in commercial aviation as determined by physiologic, medical and engineering bases.** L. D. CARLSON, W. R. LOVELACE, II, (by invitation) and H. L. BURNS (by invitation). *Dept of Physiology and Biophysics, Univ of Washington, School of Medicine, Seattle, Washington*. *Lovelace Clinic, Albuquerque, New Mexico*. *Consulting Engineer, Portland, Oregon*. Sufficient data are available to establish the physiologic requirements for oxygen in commercial aviation, though information concerning pulmonary ventilations of passengers in flight seems lacking. New commercial aviation developments necessitate the determination of the requirements for altitudes as high as 40,000 feet. "In flight" data, collected in the AAF by the authors and Dr V. J. Wulff, provide a partial knowledge of these requirements. Pulmonary ventilations which must be satisfied are set at 14 l/m up to 30,000 feet, at 18 l/m at 35,000 feet, and at 30 l/m BTPS at 40,000 feet. A lesser increase above 30,000 feet has been noted in chamber experiments by F. G. Hall, *et al*. In pressurized cabins oxygen use will be mainly in emergency, so that the flow requirements are set high to provide for a statistically determined majority (90%) of passengers. A nomogram has been prepared which states the requirements as related to continuous-flow regulator setting. Increasing the flow of oxygen above normal would protect passengers suffering from pulmonary fibrosis, emphysema, anemia, cardiac diseases, etc. Present data indicate that the administration of as little as 50% oxygen



is of value in certain clinical cases. A nomogram, prepared from standard data, indicates the flow-ventilation relationships in providing 50% to 100% oxygen at G.L. and 10,000 feet. The results are embodied in a design of a practical continuous flow system.

Studies concerning the role of metabolism in steady I.M.I. maintenance under the influence of DNP. L. D. CARSON, A. W. MARTIN, K. K. KRAMER (by invitation). *Dept. of Physiology and Biophysics, School of Medicine, Univ. of Washington, Seattle, Washington*. The interpretation of the relation of steady potentials to metabolism in living tissues is difficult due to the lack of correspondence of effects of certain substances on the two phenomena unless a specific polarity in the metabolic link is assumed, or a specific system is responsible for the potential. Additional attention must be given to those substances which provide, or influence, a phase boundary potential. Previous work has demonstrated instances where respiratory stimulants ( $H_2O_2$ ) and depressants (barbiturates) exert an analogous effect on the respiration and the I.M.I. of frog skin but over a different concentration range. This type of effect has now been demonstrated for dinitrophenol as well. Optimum concentrations for enhancement of the I.M.I. are at approximately  $5 \times 10^{-5}$  M DNP at pH 6.5 and  $6 \times 10^{-5}$  M DNP at pH 7.5. (See Rose, *Anal. Rec.*, 64: 85). The respiration of frog skin shows a maximum stimulation at pH 7.0 with  $5 \times 10^{-4}$  M DNP. This effect of DNP on the I.M.I. and the respiration of frog skin varies inversely with the degree of dissociation of the DNP molecule. The data in their present form do not justify the conclusion that the variance in effect is due to two separate respiratory systems, or to a polar effect on any systems, but it is significant that respiratory inhibitors and stimulants applied to tissues alter the R.Q., indicating a possible substrate change, and that instances have been reported where certain inhibitors have been found to block certain cell functions without disturbing the rate of metabolism.

The toxicity of delvinal sodium for both young and old rats. EUGENE B. CAMMACHAN. *Biochemistry Dept., Medical College of Alabama, Birmingham*. The toxicity of delvinal sodium has been tested for both young and old rats. The drug was dissolved in water and a fresh solution was injected intraperitoneally into normal rats. There were 369 young rats (1-9 months) and 243 old rats (9-24 months) in the series. The injections were made during several different months in order to see if there was any seasonal variation in the toxicity of this drug in this section of the country. Rats seem to be definitely more susceptible to delvinal sodium during the warm months than during the fall and winter months. The median lethal dose,

$LD_{50}$  during the summer months is about 115 to 130 mg/kg for young rats and about 75 to 95 mg/kg for old rats.

The influence of various physical therapeutic measures on the course of gravity shock. M. KATSUMI CAHY (by invitation), FRANK L. ALPHEA (by invitation) and F. A. HEFFERBANT. *Dept. of Pathology and the Baruch Center of Physical Medicine, Medical College of Virginia*. The object of this study was to observe and compare the effect of commonly used physical therapeutic measures on the peripheral circulation. The 56 experiments comprising this series are based upon fundamental observations made by one of us (F. A. H.) at the University of Wisconsin, establishing the conditions under which orthostatic circulatory insufficiency may be used as a criterion for evaluating the efficacy of clinical devices believed from a priori knowledge to augment venous return.

The subjects of the investigation were 7 healthy adults. After prolonged preliminary stabilization, the subject was moved passively to the angle known to be critical when maintained for a long enough time in a warm and quiet room by a relaxed and immobile individual. Blood pressures were determined at 60 second intervals without interruption and the heart rate was followed by continuous precordial auscultation.

The effects of massage, muscle setting, electrical stimulation and the suction pressure boot were observed as well as appropriate controls designed to differentiate between these and aberrant concomitants like psychic reaction to the procedure, and unavoidable complications associated with the technique of administering the physical agent. The independent variable was introduced either before the subject was moved from horizontality to the critical angle, at the height of the compensatory reactions, or intermittently during their course.

All the physical agents observed had a significant modifying influence on the development of gravity shock of common physiological origin, rapidly effective in a recuperative way and varying primarily in ease of administration.

Effect of caloric restriction on the development and function of adrenal cortical tumors in mice. CAROL B. CASAS (by invitation), JOSEPH T. KING, and M. B. VISSCHER. *Dept. of Physiology, Medical School, Univ. of Minnesota*. It is known that the ovariectomized  $C_3H$  mouse develops adrenal cortical tumors. The vaginal smear and the histology of the vagina and uterus show that the animal has been subjected to estrogenic stimulation.

It is also known that the underfed, intact rodent develops an anestrus which has been interpreted as due to pituitary inhibition since the animals respond to gonadotropin.

It was thought that caloric restriction might prevent the development of the adrenal tumors



which are presumably the source of endogenous estrogen

Ovariectomized C<sub>3</sub>H mice were restricted to 66% and to 50% of the caloric intake of litter mate controls. The absolute amount of protein, vitamins, and minerals was not restricted.

The only effect of restriction on the development of the tumors was a slight delay. After 100 days on the diets the tumors in the restricted and full-fed mice were essentially identical.

However, the restricted mouse shows no evidence of estrogenic stimulation.

It is apparent that although the tumors are histologically identical their effect is not the same in the restricted and full-fed mouse.

**Cellular distribution of glycoprotein in the anterior lobe of the pituitary gland.** HUBERT R. CATCHPOLE, *Dept of Pathology, Univ of Illinois College of Medicine*. Using the Hotchkiss technique of visualizing polysaccharide or polysaccharide complexes, a carbohydrate material was demonstrable under certain conditions in cells of the anterior pituitary gland. In view of the apparent glycoprotein nature of pituitary gonadotrophic hormones (cf Chow, *Advances in Protein Chemistry*, I, 1944), glands in various stages of physiological activity were studied. Material was obtained from adult female rats during the oestrus cycle, pregnancy, and following castration, from normal and castrated adult male rats, and from female rabbits before and after mating.

Preliminary studies showed a glycoprotein material to be associated with granules of castration cells. This was soluble in 2 per cent sodium chloride in the cold, 5 per cent aqueous pyridine, 33 per cent ammonium sulfate, 60 per cent alcohol, and acetate buffer at pH 4.0, insoluble in saturated ammonium sulfate, 80 per cent alcohol, 80 per cent acetone, and acetate buffer at pH 4.5.

**"Secondary photosensitization" of hydra fusca after exposure to methylcholanthrene.** H. W. CHALKLEY and GEO. E. DANIEL (by invitation), *National Cancer Inst., Bethesda, Maryland*. Hydra fusca after exposure to dilute aqueous suspensions of methylcholanthrene is sensitive to radiation in the near ultraviolet. This sensitization is lessened by washing for four hours after exposure. However, if the washing is continued for twenty-two hours the sensitivity rises above that found after four hours washing. Tentatively this use has been designated "Secondary photosensitization." An explanation is being sought. It is suggested that phenomena of this type may be associated with long retention of sensitivity in other forms.

**Asynchronism of ejection of the ventricles as measured with the electrokymogram.** W. EDWARD CHAMBERLAIN (by invitation), BERT R. BOONE (by invitation), GEORGE F. ELLINGER (by invitation), GEORGE C. HENRY (by invitation) and MORTON J.

OPPENHEIMER, *Depts of Radiology, Medical Physics and Physiology, Temple Univ School of Medicine, and Heart Demonstration Section, U S Public Health Service, Philadelphia, Penna.* The development of the electrokymograph (Amer J Roentgenol 54:217, 1945) provides a new method for studying the contraction of the ventricles and pulsation of the great vessels in man. When the aperture of the electrokymographic pickup is aligned with the fluoroscopic silhouette of the pulmonary artery near its origin, the resulting tracings may be compared with those obtained from corresponding points on the ascending aorta.

Normal young adults were studied in this way. In a majority of these the ejection of blood from the ventricles was asynchrous, with either right or left ventricle leading by varying times up to 0.03 second. In a few cases ejection was synchronous.

The electrokymograms for these studies were made in two ways: (1) With a single pickup device and simultaneous recording of the carotid pulse, the pulmonary artery and aorta were studied consecutively instead of simultaneously, using the carotid pulse tracing as a reference curve on the time axis. (2) With two separate pickups and two galvanometers, simultaneous records from both great vessels permitted direct comparison.

For both methods the possible errors are discussed. Applications to the study of right and left bundle branch block are presented.

**A method and observations on capillary fragility in rabbits.** ROBERT CHAMBERS and ALFRED L. COPLEY, *Laby of Cellular Physiology, Dept of Biology, New York Univ, New York*. The method for measuring capillary fragility is based on the effect of hemorrhagic agents locally applied to minute vessels under microscopic observation. The degree of resistance of these vessels to the formation of petechiae is used as an index of capillary strength.

The vessels of the nictitating membrane of the rabbit's eye were chosen for the observations. The technique involved ascertaining the minimum effective concentration of a given hemorrhagic agent locally applied. The control test was first made on one eye, and subsequently on the other eye after the systemic injection of a substance to be investigated.

One-twentieth of a cc of a given agent was injected intradermally with a 27 gauge needle. The membrane was then kept under microscopic observation and the time of appearance of the first petechia was noted. Thereafter, the number of developing petechiae was recorded at intervals of 5 to 15 minutes over a period of 3 hours. The rabbits could be classified into susceptible and resistant groups.

The locally applied agents were high dilutions of sodium merthiolate, purified Shiga protein toxin,

croton oil, etc. With systemic injection of sodium heparin it was found that 25 mgm per kilo increased the petechial count significantly. Several other substances also have been tested [aided in part by a grant from the American Medical Association].

Site of action of a bacterial pyrogen in rats with central nervous system lesions. WILLIAM W. CHAMBERS (by invitation) and WILLIAM F. WINDL, *Univ. of Washington Medical School, Seattle*. Injection of 25  $\mu$ g purified pyrogenic extract (from *Pseudomonas aeruginosa*) per kg in rats, while variable, generally led to the following sequence of events. Drowsiness appeared immediately, rectal temperature increased with piloerection, and usually with mild shivering, during the second half hour. By the end of one hour, the febrile response averaged 2° F, drowsiness and piloerection continuing, but shivering ceasing. The febrile peak was attained by 4 hours, averaging 3.6° F, thereafter, piloerection disappeared. Temperature began to fall after the peak and reached normal by 8 hours.

To try to determine site of action of the pyrogen, bilateral caudal hypothalamic lesions were produced with the Horsley Clarke instrument, interrupting hypothalamic thermoregulatory pathways. In others, transection was produced in the cervical spinal cord. Normal temperature was maintained and little change in weight occurred.

Chronic hypothalamic lesion animals were unable to adjust to sudden environmental temperature changes. They consistently gave febrile responses to the pyrogen, but piloerection and shivering were absent. Chronic spinal animals showed marked inability to adjust to sudden environmental temperature changes. They repeatedly gave no response to the pyrogen.

Representation of cutaneous tactile sensibility in the cerebral cortex of the spider monkey. H. T. CHANG (by invitation), C. A. WOOLSEY, L. W. JARCHO (by invitation) and E. HENNEMAN (by invitation). *Dept. of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore 5, Md.* The tactile area of the postcentral gyrus has been mapped in the spider monkey by the evoked potential technique in terms of the cutaneous area related to each cortical point examined. In a single experiment conducted over a period of 58 hours, the investigators working in pairs by rotation explored the responsive portion of the postcentral cortex in 2 mm steps from midline to sylvian fissure with the following results.

1 The basic plan of organization is the same as that described earlier for *Macaca mulatta* and for other mammalian forms.

2 There is a large area for the tail which extends for 5 to 6 mm lateralward from the medial edge of the hemisphere.

3 Associated with the marked development of

the tail area there is a striking lateral displacement of the rest of the tactile area, with the result that the finger area reaches the sylvian fissure and the face area has apparently become almost entirely hidden within the fissure.

4 Although the thumb is absent in this monkey, it is of interest that the skin of the thenar side of the hand is well represented in that portion of the hand area which in *Macaca mulatta* subserves the thumb.

5 The amount of cortex devoted to arm, trunk and leg is approximately the same as in the macaque.

Threshold bleeding and the sex skin in the castrate female chimpanzee. GEORGE CLARK, *Primates Laboratories of Primate Biology, Inc. and Yale Univ.* In the castrate moneaque periodic bleeding under constant but low dosage of estrogen has been reported. Under similar conditions of therapy in the castrate mouse and rat there may occur periodic flooding of the cornified smear with leucocytes. It has been tempting to ascribe these results to fluctuations in output of sex hormones by the adrenal gland. In the female chimpanzee there are two external indicators of cyclic activity—the changes in size and configuration of the sex skin and menstrual flow. Under constant dosage with an estrogen and a progestin periodic changes in both these organs occur. The precise relations between the sex skin swelling and bleeding do not remain constant, however, and it is therefore suggested that the cyclic activity cannot be due to fluctuations in output of adrenal hormones.

The effect of diisopropyl-fluorophosphate upon the response of the turtle heart to vagus stimulation. SAUL L. CONEY<sup>1</sup> (introduced by Robert Gesell). *Physiology Lab., Univ. of Michigan, Ann Arbor*. Replacement of the pericardial fluid by approximately 0.0004 M diisopropyl-fluorophosphate (DFP) in Ringer's solution had no effect on the normal rhythm of the heart, but caused a marked increase in the degree of inhibition effected by stimulation of the vagus nerves to the heart. In the presence of DFP short periods of right vagus stimulation repeated at regular intervals resulted in an increasing inotropic effect on the right auricle, a much lesser increase in inotropic effect on the left auricle and in an increasing chronotropic effect on all three chambers. Responses to left vagus stimulations showed similar changes, with the inotropic effects being most marked for the left auricle and with the chronotropic effects developing much more slowly. These effects of DFP persist even 2 hours after removal of the DFP and frequent washings of the heart with Ringer's solution. These results are readily

<sup>1</sup> Present address: Department of Physiological Chemistry, University of Minnesota, Minneapolis.

explained on the basis of an irreversible inhibition of the cholinesterase at the heart vagus endings by DFP and on the basis of the generally accepted distribution of fibers from the right and left vagus nerves to the heart of the turtle. The partial recovery of the heart from the effects of vagal stimuli indicates that even in the presence of DFP the acetyl choline is being slowly removed. The gradual decrease in the degree of recovery with repeated nerve stimulations may be due to a relatively slow rate of choline esterase inhibition by DFP in the concentrations used here.

**Preliminary studies of the assay of hypertensin (angiotonin)** DEAN A. COLLINS *Depts. of Physiology of the Univ. of Illinois, College of Medicine and of Temple Univ., School of Medicine*. Collins and Hamilton (Am J Physiol 140:499, 1944) used the responses of guinea pig ileum, in aerated Tyrode with atropine at 38°C, for the assay of plasma hypertensin. The present studies were undertaken in an attempt to increase the reliability of this assay. The following modifications have been found helpful. The best length of the loaded gut (700 mgm) was found to be 4-4.5 cm. After 3 minutes for contraction, the muscle was washed and rested 5 minutes. Greatly increased consistency in responses resulted from washing the ileum without draining the muscle chamber. Tyrode was run into the lower end of the chamber through a side-tube and the overflow drawn off by suction.

Heparinized plasma, after incubation with renin, was brought to pH 5 with HCl and heated at 90-95°C. Coagulated protein was removed by centrifugation. Recovery experiments indicated minimal loss of hypertensin. Further purification was indicated while the gut responded to about 1 unit of hypertensin (unit of Braun-Menéndez et al) in 750 ml (confirming Ludueña, Rev Soc argent de biol 16:358, 1940), it responded to heated plasma without hypertensin at a threshold dilution of about 1 to 25. Thus the gut could not be used to detect plasma concentrations of less than approximately 3½ units per 100 ml. No completely satisfactory purification has yet been found. Methanol ethyl ether purification of heated plasma reduced non specific stimulating properties about 40% and hypertensin activity about 15%.

**Neutralization by tubulin (renal antipressor substance), of vasoconstrictor action of epinephrin on frog** OTIS M. COPE and BENJAMIN JABLON (by invitation) *New York Medical College, Flower & Fifth Ave Hospitals*. The effect of epinephrin both locally and after injection into the lymph sac of the frog (*Rana pipiens*) is to constrict the peripheral circulation which is manifested by an increasing sluggishness of the blood flow in the capillary network, a-v vessels, metarterioles, arterioles, smaller arteries and veins, in

order named. This is followed by complete arrest of the blood flow lasting from several minutes up to one hour.

Tubulin administered, locally or by injection, neutralizes this vasoconstrictor effect. It also protects against the subsequent injection of epinephrin when given fifteen to twenty minutes after tubulin administration.

Pithed frogs of medium size injected with 1.0 cc of tubulin equivalent to 2.5 grams of whole kidney tissue were studied under the capillary microscope. Areas examined were in the interdigital web of the frog foot and the retro lingual membrane. 0.1 to 0.5 cc of a  $\frac{1}{1000}$  epinephrin solution were injected into the lymph sac to determine the duration of the vasoconstrictor effect. Tubulin was then administered and after an interval of fifteen to twenty minutes reestablishment of blood flow was observed. In many instances blood flow was more accelerated than the normal. Subsequent administration of epinephrin in five times the amount sufficient to produce vasoconstriction failed to slow the circulation or produce any appreciable narrowing of the blood vessels.

Administration of tubulin immediately after circulation had been arrested by epinephrin brings about blood flow return in reverse order from that described above viz the small arteries, arterioles, metarterioles, and capillary network.

**The clotting of limulus blood** ALFRED LEWIN COPLEY *Marine Biological Lab., Woods Hole, Mass. and Lab. of Cellular Physiology, Dept. of Biology, New York Univ., New York*. The blood of *limulus polyphemus* does not contain fibrinogen and therefore represents a good source for studying cell agglutination. As already described by Leo Loeb two phases of clotting can be observed: agglutination of amoebocytes and gelation of the whole blood. These processes can be easily timed macroscopically using glass slides or test tubes. Agglutination times were found to vary from 6 to 20 seconds. Gelation times, measured by the first appearance of a gel, ranged from 24 to 55 seconds. Syncresis occurred in all the samples.

Sodium heparin in excessive amounts in vitro and in vivo neither inhibited the agglutination of amoebocytes nor the subsequent gelation. Sea water and isotonic potassium chloride decreased, whereas distilled water tended to increase the agglutination time. Low temperature (0°C) as compared with room temperature (20-25°C) prolonged the agglutination time but did not affect significantly the gelation time. Agglutination and gelation times were only slightly prolonged with the use of equipment coated with methyl-chlorosilane (General Electric Dri-Film 9987).

Salts of rare earths in concentrations of 100 gamma/cc blood affected neither agglutination nor gelation. Cerous sulfate in 0.26 M concentration,

isotonic with sea water, did not inhibit clotting. At same molarity neodymium acetate prolonged the agglutination time and inhibited gelation, while neodymium chloride and lanthanum nitrate inhibited clotting completely. However, upon diluting the two latter blood rare earth systems with distilled water, the macrocytes became agglutinated. The same phenomenon was observed by diluting blood to two third saturated ammonium sulfate solution. The macrocytes could thus be isolated, however upon addition of water they agglutinated readily. [Aided in part by a grant from the Lilly Research Laboratories.]

Effect on renal function of rats of substances containing vitamin A. A. C. CONNOR and IRVING H. PAGE. With the Assistance of A. Buckingham. From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio. A renotropic property of concentrates containing vitamin A has been reported in human beings, dogs and rats. Our observations in human beings indicated that the activity of the concentrates is reproduced by oral dosage with crystalline vitamin A or natural tocopherols, but that it is due to a substance which like these, is photo and thermolabile.

In attempting to identify this material, we have used tubular secretory capacity for p-aminohippuric acid (TMPAH) in rats as the criterion of activity. Crude vitamin A concentrates increase this function by 100 per cent during 16 weeks of dosage with 2000 I.U. per day intramuscularly and half of the effect persists for 12 weeks after discontinuing treatment. Crystalline vitamin A (2 mg per day) and neovitamin A (2000 I.U. per day) are inactive, as is one fish-oil concentrate rich in vitamin A. We conclude that the renal effects of treatment with vitamin A are not due to the vitamin as such.

In the course of the study a comparison was made of glomerular filtration rates in normal rats of the Sprague-Dawley strain and in a group largely composed of rats of a Wistar strain. The mean levels and variability of glomerular filtration rates were the same in both groups. In contrast the mean level of TMPAH in rats of the Sprague-Dawley strain was found to be significantly higher (mean 3.27 mg per kg per min.) than in the other group (mean 2.36 mg). The difference of the means of TMPAH divided by the standard error of the means of the two groups is 4.6.

We thank Dr. Phillip Harris, Distillation Products, Inc., for his generous assistance.

Tests on explosive decompression. L. L. CONNOR. Univ. of Virginia. Apparatus was constructed for explosively decompressing animal chambers to an alt. equivalent of 80,000 ft. 300 tests on rats and cats have been carried out to date. Recompression was carried out usually at a rate to simulate that of a freely falling man (av. 200 m.p.h.) until the

18,000 ft. level was reached, thereafter a fall of 20 f.p.s. was maintained, simulating that of parachute descent.

No fatal injuries were observed in explosive decompression below 35,000 ft. From this level up to 80,000 ft., slightly more than 50% of the animals succumbed. Even at the latter level, however, a few animals survived following very rapid recompression. Injuries produced were limited to the lungs and gastro-intestinal tract. Pulmonary hemorrhage and bleeding into the gastro-intestinal tract with occasional perforations were observed. In cases of fatal decompression the heart rate fell progressively, with arrhythmia, block, decrease in R spike potential and abnormality of the T wave.

The severity of the injury from explosive decompression would appear to depend on (a) the volume of gas within the lungs (i.e. phase of respiration) and gas tract at the moment of decompression, and (b) the length of time the animal is maintained at the simulated (high) altitude.

A striking observation was that in all cases in which filling of the lungs was restricted by a simple strip around the upper part of the body, no fatality occurred from explosive decompression. Also in tests in which very rapid ("instantaneous") recompression was made, a much larger number of animals survived. [Work carried out under a contract between U. S. Navy, Office of Naval Research, and the University of Virginia.]

Measurement of total and bicarbonate base of urine by the cation resin-exchange and electro-dialysis methods. SAMUEL A. CORSON and OTTO C. CLARK (by invitation). Dept. of Physiology, Univ. of Minnesota School of Medicine, Minneapolis. The total base was determined by Keys' electro-dialysis method. In urine samples dialysis was complete in 20 minutes in contrast with the experience of Polis and Reinhold with serum where as much as 18 hours were required for complete dialysis. This difference is probably due to the absence of proteins from the urine. The non-bicarbonate base was determined by the cation resin adsorption method. The difference between the two values represents the base bound by bicarbonate. This method is more simple and less time consuming than the Van Slyke method and has an accuracy of  $\pm 1\%$  for base values usually encountered in urine samples.

The mechanism of diuretic action of salts of organic acids. SAMUEL A. CORSON, ELINOR FOSTER (by invitation), ELIZABETH RADWAY (by invitation), and JAMES O. ELANI (by invitation). Dept. of Physiology, Univ. of Minnesota School of Medicine, Minneapolis. Experiments on anesthetized and unanesthetized rats, dogs, cats, and rabbits in the post-absorptive state demonstrated that oral,

<sup>1</sup> This work was supported in part by a research grant from Hospital Liquids, Inc.

intraperitoneal, or intramuscular administration of sodium salts of organic acids produced diuretic effects superior to equimolar concentrations of neutral or acid salts, urea, and the usual therapeutic doses of xanthine or mercurial diuretics. The diuretic effects were comparable to or better than isosmotic concentrations of urea or KCl and definitely superior to isosmotic concentrations of  $\text{NH}_4\text{Cl}$ .

When given intravenously, the salts of organic acids invariably produced more diuresis than isosmotic concentrations of neutral salts. Similar results were observed in rats with experimental temporary "ascites" produced by intraperitoneal administration of a gelatin saline solution having an oncotic pressure of 7-10 mm Hg. Diuretic effects of the same order of magnitude found in normal animals were observed in dogs with experimental nutritional edema following the intravenous administration of hypertonic solutions of sodium succinate. This diuresis is probably due to the osmotic effects of succinate in the kidney tubules and the excretion of base following metabolic transformation of most of the injected succinate. Twelve to 43% of the injected succinate could be recovered in the urine depending on the quantity injected.

That the excretion of base contributed significantly to the diuretic effects is demonstrated by the following facts: 1) Monobasic salts of succinate or fumarate or the free acids possessed very much less diuretic potency than the dibasic salts. 2) The pH of the urine excreted in response to salts of organic acids was progressively increased, though in most cases this pH increase was delayed. 3) The diuretic effects of dibasic and monobasic salts were roughly directly proportional to the quantity of base injected. Potassium salts of organic acids proved to be not much better diuretics than the corresponding sodium salts.

**Mechanism underlying cardiac output change during intermittent positive pressure breathing (IPP)** ANDRE Cournand, HURLEY L. Motley (by invitation) and LARS WERKO (by invitation) *Dept. of Medicine, College of Physicians and Surgeons, Columbia Univ., New York City*. Since cardiac output variations during IPP are related to form and amplitude of mask pressure changes, and inspiratory-expiratory time ratio, a study was made of right intraventricular pressure tracings during ambient and IPP in an attempt to analyze the underlying mechanism.

The beat to beat right intraventricular pulse pressure variations were studied in 30 men with essentially normal circulation. In 5 individuals intrapleural pressures were obtained and related to simultaneously calculated net filling pressures (end diastolic minus pleural pressure). Because

IPP changes pulmonary vascular resistance, interpretations of pulse pressure variations in terms of stroke volume changes were often equivocal. However, the curves of net filling pressures, although in phase with, varied inversely as pleural pressure. Since pulmonary vascular resistance does not influence net filling pressure, the above changes were interpreted, in accord with Starling's Law of the Heart, as indicating stroke volume variations.

With all types of mask pressure curves, the net filling pressures were lower during periods of increasing intrapleural pressure with IPP than during ambient breathing. The reverse occurred during the period of decreasing intrapleural pressure when these curves showed an early rapid drop in pressure.

The analysis demonstrates that mean cardiac output remains unchanged when the number of systoles with increased stroke volumes associated with decreasing pleural pressure compensates for the deficit occurring during the increasing pleural pressure phase. Inspiratory-expiratory time relationship and the expiratory curve form are therefore the main features to consider for improving mechanical devices designed for maintaining artificial respiration. [Aided by contract with Aero Medical Laboratory, Wright Field, and grant from the Commonwealth Fund.]

**Sources for hepatic glucose production in fasting normal and diabetic dogs** L. A. CRANDALL, JR., ALAN LIPSCOMB (by invitation), and S. B. BARKER, *Dept. of Physiology, Univ. of Tennessee, Memphis, Tennessee*. During investigations into hepatic glucose production in normal and diabetic fasting dogs (*Amer. Jour. Physiol.* in press), determinations were also made of hepatic retention of lactic acid and output of urea and acetone bodies in unanesthetized dogs several weeks or months after the angiotomy operation by the technique of London.

Calculations of glucose available for gluconeogenesis assume that (1) 100 per cent of the lactic acid is convertible into glucose, (2) amino acids deaminized in the liver equal urea nitrogen eliminated times 6.25, and 58 per cent of these are converted into glucose, (3) all carbon atoms of fatty acids are converted into acetone bodies and the glycerol from these fats is entirely available for gluconeogenesis.

On the basis of these calculations, the glucose available from these sources in fasting normal dogs amounted to 92 per cent of the glucose actually liberated (13 determinations), and in diabetic dogs three or more days after withdrawal of food and insulin the calculated available glucose amounted to 103 per cent of the glucose actually liberated, (11 determinations). In both types of animals, lactic acid and amino acids accounted in approxi-

mately equal proportions for about 90 per cent of the glucose where is glycerol accounted for 30 and 64 per cent of the glucose in normal and diabetic dogs respectively.

Since these precursors can account for all glucose produced there is no evidence for gluconeogenesis from other sources.

**Production of regional ischemia by intravascular injection of glass and plastic microspheres in graded sizes.** J. M. CUMMINS and L. A. LUNNAN, *Dept. of Physiology, Stanford Univ. School of Medicine.* A method involving the intra-arterial injection of inert, microscopic emboli has been developed for studying the relationship between size of vessels, obstructed blood flow, and tissue damage. Microscopic spheres of glass and of isobutyl methacrylate were graded by subjecting all particles which passed through a 140 mesh screen to further separation by water elutriation. The sphere diameters in individual samples covered a range of approximately 20 microns, the smallest being 25 to 35 microns and having a mean diameter of 35 microns. Seven samples were prepared with mean diameters 10 microns apart between 35 and 95 microns. Introduction of the spheres into various restricted arterial distributions in rabbits has been accomplished by passing a #4 French ureteral catheter into the right carotid artery and down the aorta to a point opposite the desired major branch. The aorta is occluded by external manual compression during the injection. With the aid of metal clips placed at a previous operation and radio opaque suspension medium, fluoroscopic visualization permits accurate placement of the catheter tip.

Introduction of microspheres into the femoral blood stream of rabbits by central injection into the saphenous artery is followed by decline of skin temperature in the foot. Usually within two hours the skin temperature of the foot on the obstructed side rises and may exceed that of the opposite foot. This sign of reactive vasodilatation and increased blood flow was not repeated following a second injection of spheres.

**The acid factor in the production of gastrointestinal ulcers in dogs.** G. M. CUMMINS (by invitation), M. I. GROSSMAN, and A. C. IYR, *Dept. of Physiology, Northwestern Univ. Medical School (now at Univ. of Illinois College of Medicine).* Continuous gastric perfusion of 0.1N isotonic HCl per gastrostomy (71 to 83 cc per hour) resulted in the development of duodenal or gastric ulcerations in from 50.5 to 90 hours in all of 5 dogs. Severe acidosis in all of these animals was evidenced after 12 hours by vomiting and weakness, blood pH determinations on 2 of the dogs were 7.14 and 7.10 after 33 and 52 hours respectively. Four more dogs were also given 0.16N  $\text{NaHCO}_3$  by continuous drip

per terminal ileostomy in addition to acid by gastrostomy and maintained normal acid base balance as judged by daily blood pH determinations, these animals ate well and developed no ulcers after from 39 hours to 12 days. Two additional dogs in this series were fasted, one showed no ulcer after 80 hours and the second, after developing an acidosis due to inadequate introduction of base (the blood pH dropped to 7.25) revealed a duodenal ulcer after 54.5 hours. To eliminate the possibility of regurgitation of base into the upper gastrointestinal tract 0.16N  $\text{NaHCO}_3$  was introduced by continuous intravenous drip in 3 fasted dogs receiving acid per gastrostomy, normal blood pH levels were maintained and no ulcers were found when sacrificed after from 74 to 77 hours. These studies show that continuous gastric perfusion of physiological amounts of HCl will consistently produce ulceration of the upper gastrointestinal tract in dogs and that the prevention of the systemic acidosis that results from such acid introduction will annul the ulcerogenic effect of the acid.

**A basis for interpreting autonomic-EEG relationships.** CHESTER W. DARROW and CHARLES E. HENRY (by invitation), *Inst. for Juvenile Research, Chicago.* Records of 400 individuals were examined to determine empirically autonomic measures providing best separation of EEGs with respect to pattern, voltage and frequency. As a result of this exploration representative motor and motor-parietal area EEG samples were distributed with respect to the three degrees, high, medium and low for the 5 variables, resting reclining heart rate, systolic blood pressure, palmar skin conductance (sweating), palmar conductance change during hyperventilation, and relation of immediate recovery (3 seconds) to immediately preceding conductance reaction to stimulation. The tendency for higher voltage and slower EEGs to accompany faster heart rates is confirmed and some of the exceptions to the rule accounted for as reported elsewhere on this program. High voltage slow activity appears possible in the relative absence of palmar sympathetic tone (low conductance) but high voltage rhythmic EEG activity depends upon appreciable sympathetic tone or capacity for its arousal during activity. Subcortical mechanisms are presumably here involved in maintaining both resonance and sympathetic activity. Low voltage fast EEG activity predominates among individuals with slower heart rates or higher blood pressures. Lower voltage faster bipolar (cortical cortical) than unipolar (cortical subcortical?) patterns suggestive of strong cortical activity tend to characterize individuals having large relative immediate recovery following palmar sympathetic reaction. Clinical

differentiation of cases with respect to these variables will be briefly outlined

The protective action of thyroid and potassium iodide in cholesterol induced atherosclerosis in chickens D DAUBER<sup>1</sup> (by invitation), L HORLICK<sup>2</sup> (by invitation) and L N KATZ *From the Cardiovascular Dept., Research Inst., Michael Reese Hospital, Chicago, Illinois* <sup>3</sup> Dauber and Katz have reported the induction of aortic atherosclerosis in chickens by the addition of cholesterol to the chicken mash. In view of the results obtained by others in inhibiting the production of cholesterol induced atherosclerosis in the rabbit by the simultaneous administration of thyroid or KI, it appeared to be of interest to ascertain whether similar results could be obtained in the chicken

Six week old Leghorn chicks were fed a diet of chick starter mash in which was incorporated 2% cholesterol in 20% cottonseed oil. After 11 weeks of feeding and treatment, gross and microscopic examinations were made of the aortas, hearts and thyroid glands. Three groups each consisting of sixteen birds were utilized. Group I, the control chickens showed aortic intimal atherosclerosis in every instance. Group II, received desiccated thyroid by mouth (50-200 mg/kg/day). Two birds of this group were completely free of atheromatous lesions. Group III received KI by mouth (200-800 mg/kg/day) and three of these birds were completely free of lesions. In the remainder of Groups II and III lesions of varying degree of severity, similar to those in the control group were seen.

The oxidative metabolism of the mouse stomach HORACE W DAVENPORT *Dept of Physiology, Univ of Utah School of Medicine, Salt Lake City* The oxidative metabolism of the fundic portion of the mouse stomach including mucosa and muscularis was studied using the Warburg technique and standard analytical methods. The average  $Q_{O_2}$  over a two hour period without added substrate is 6.4. With 0.02 M substrates it is 6.6 with glucose, 6.2 with lactate, 5.7 with pyruvate, 5.5 with acetate and 4.9 with fructose. The  $Q_{O_2}$  is reduced to 0.9 by 0.01 M cyanide, to 2.1 by 0.01 M iodoacetate and to 2.7 by 0.00034 M arsenite. The mucosa disintegrates in the presence of cyanide and iodoacetate but not in the presence of arsenite. The addition of glucose, lactate or pyruvate does not reverse any of the inhibition. Without substrate the stomach produced 0.021 micromols lactate per mg dry weight per hr. With glucose, fructose or pyruvate substrates the lactate production is 0.116, 0.034 and 0.120 micromols per mg

dry weight per hr respectively. Only traces of pyruvate appear in the absence of arsenite. Pyruvate accumulates in the presence of arsenite, and if the amount accumulating were completely oxidized it would account for  $1\frac{1}{2}$  times the oxygen uptake deficit produced by arsenite. The metabolism of the stomach is not detectably affected by histamine or urogastrone either in the fluid medium or injected into the mice before death. [Aided by a grant from the John and Mary R Markle Foundation]

Cortical excitability in pyridoxine-deficient rats VIRGINIA D DAVENPORT (by invitation), HORACE W DAVENPORT, and LOWELL A WOODBURY (by invitation) *Dept of Physiology, Univ of Utah School of Medicine, Salt Lake City, Utah* In 22 pyridoxine-deficient rats and 24 pair fed controls the correlation between body weights and electroshock thresholds were +0.85 and +0.81, respectively. In the deficient rats the mean changes in electroshock threshold 5 and 24 hours after a subcutaneous dose of 5 mg pyridoxine as compared with the threshold immediately prior to injection were +2.9 and +3.2 mA, respectively. The changes were significant ( $p < 0.01$ ). In the control rats the changes 5 and 24 hours after pyridoxine were -0.1 and +0.2 mA, respectively. The changes were not significant ( $p > 0.3$ ). The rise in threshold in the deficient rats was roughly correlated with the presence and amount of vanthuenic acid in the urine during the period of deficiency. The Metrazol thresholds were judged by the appearance of a typical EEG pattern of high voltage spike and dome complexes and subsequent depression following subcutaneous injections of Metrazol. The pyridoxine-deficient rats had a mean Metrazol threshold of 47 mg per kg, and after a dose of 5 mg pyridoxine the threshold rose about 65%. The change was significant ( $p < 0.02$ ). In the controls there was no change in Metrazol threshold after pyridoxine. There were no differences between the resting EEG pattern of the control and the deficient rats, and the EEG pattern during Metrazol convulsions were the same. [The work described in this paper was assisted by a research grant-in-aid of the U S Public Health Service]

The application of flame photometry to sodium and potassium determinations in biological fluids A K DAVIS (by invitation) and RICHARD R OVERMAN *Dept of Physiology, Univ of Tennessee College of Medicine, Memphis* The necessity of separating Na and K prior to their quantitative determination by the various chemical methods has led to procedures which are often prohibitively tedious and time consuming in biological research. The recent development of flame photometry has now made possible physical methods of analysis in which chemical separation of these elements is

<sup>1</sup> Deceased  
Dazian Fellow

<sup>2</sup> Supported by a grant from the Life Insurance Medical Research Foundation



unnecessary (Barnes, et al *Ind and Eng Chem* 17 605, 1945)

The present report concerns the use of the Model 15 Perkin Elmer Flame Photometer in Na and K determinations on blood plasma, red cells and urine. The instrument is first calibrated using solutions of known concentrations of Na and K in similar relative proportions to those found in the biological fluids to be tested. Blood, plasma and red cells are prepared for flame photometric determination by dilution (and consequent laking of red cells) with distilled water and precipitation of proteins with trichloroacetic acid. Subsequent centrifugation yields a filtrate which is ready for Na and K determinations directly. Urine is simply diluted to optimal Na and K concentrations for flame photometric analysis.

By taking multiple readings on each unknown and by frequent checking of the zero and 100 per cent point on the vernier, the accuracy of the method is  $\pm 3$  per cent of the amount of Na present and  $\pm 2$  per cent of the amount of K present. Thus the accuracy of flame photometric determination approximates that of the more laborious microchemical methods. [Research supported by grants from the Office of Scientific Research and Development and the U. S. Public Health Service.]

The influence of folic acid on serum cholinesterase activity in human subjects JOHN F. DAVIS and WILBUR M. HAMMON (by invitation) *Univ of Arkansas School of Medicine*. Recent work has indicated that acetylcholine can produce an anemina which may be abolished by the administration of liver extract or pteroyl glutamic (folic) acid (*Am J Physiol* 147:404, 1946). Although some evidence was presented to show that folic acid may increase cholinesterase activity of the blood serum, it seemed advisable to test this action further by administering this vitamin to a number of human subjects. Cholinesterase activity was estimated by an electrometric titration method described in the above reference.

Nine human subjects were given a single oral dose of 15 mgm of synthetic folic acid, immediately after the cholinesterase activities of their blood sera had been determined. Five hours after the administration of folic acid, all of the subjects showed increases in their cholinesterase activities. The increases varied from 14.3 to 32.3 per cent in the nine people, and were significantly greater than the usual daily, or day to day, variations occurring in humans and dogs.

The use of the spectrophotometer for measuring changes in skin reflectance in Rana Pipiens G. G. DEANIN (by invitation) and F. R. STEGGERDA *Dept of Physiology, Univ of Illinois, Urbana, Illinois*. By placing the dorsal surface of the unanesthetized frog before the aperture (1 inch in diameter) of the recording Spectrophotometer,

the per cent reflectance of the skin in each wave length of the visible spectrum can be recorded. The method offers an improvement over older photoelectric methods, since the change in reflectance of the skin for a particular color can be noted as the melanophores constrict or expand. Whereas the photoelectric cell measures the sum of all reflected light, the Spectrophotometer measures the reflected light in each wave length separately.

The results indicate that while melanin dispersion does not materially change the degree of reflectance in the violet blue end of the spectrum, there is a marked reduction in skin reflectance for the remaining colors of the spectrum.

Further experiments point to the fact that individual melanophores exert an all or none behavior, and that increased darkening or paling of the skin is due to the response of a greater number of melanophores rather than an increased response in the individual cells.

The relationship of insulin hypersensitivity to increased sugar utilization RICHARD C. DE BODO and KATHARINE F. PRESCOTT (by invitation) *Dept of Pharmacology, New York Univ College of Medicine, New York*. It has been suggested that the hypersensitivity to insulin observed in the hypophysectomized animal is due to an increased sugar utilization. Russell found twice the normal rate in the hypophysectomized rat.

In order to test this hypothesis normal dogs, kept on a standard diet, were made to perform moderate muscular exercise during the post absorptive state by running on a treadmill for three hours at four miles per hour. The R.Q. varied from 0.86 to 0.91 during the basal period, from 0.77 to 0.81 during exercise and from 0.74 to 0.80 during recovery. The heat production, calculated from the oxygen consumption, increased four to five times during the exercise period and returned approximately to the basal figure during recovery.

The calculated sugar utilization during exercise was four to five times the basal value. However the dogs were not hypersensitive to insulin. Our previous work showed that resting hypophysectomized dogs in the postabsorptive state exhibited hypoglycemic shock after intravenous administration of 0.025  $\mu$ /kg of insulin. On the other hand normal exercising dogs required at least 1.5  $\mu$ /kg of insulin intravenously before exhibiting a sustained fall of the blood sugar curve similar to that of the hypophysectomized animal with 0.025  $\mu$ /kg.

It is concluded that increased sugar utilization by itself is not sufficient to explain the hypersensitivity to insulin in the hypophysectomized dog. [Aided by grants from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association and from the New York Diabetes Association, Inc.]

Stimulation of area 13 and skin temperature



changes following its ablation J M R DELGADO (by invitation), J F FULTON and R B LIVINGSTON (by invitation) *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn* In monkeys (*M mulatta*) the effect of electrical excitation of area 13 on the orbital surface of the frontal lobe (Walker, *J comp Neurol*, 1940 73 59) in acute experiments has been studied The orbital surface is exposed after enucleation of the eye and removal of the orbital roof Electrical stimulation with bipolar electrodes using moderate intensities results in almost instantaneous effect on respiration It is possible to arrest respiration during any part of the inspiratory cycle A brief stimulus occurring before the beginning of inspiration results in diminished amplitude and delay in the following respiratory cycles The effects are related to the intensity of the stimulation, low intensities resulting in decreased amplitude, and often in the rate of respiration Higher intensities result in complete arrest of respiration followed by "escape" (Bailey and Sweet, *J Neurophysiol*, 1940, 3 276) In some experiments the stimulation of area 13 produced a sudden but moderate fall in blood pressure followed by a slow rise This effect appears to be independent of the mechanical effects of respiration on blood pressure

In chronic experiments in which area 13 has been ablated bilaterally the temperature of the extremities becomes higher than in normal monkeys This elevation of temperature did not follow unilateral ablation [*Aided by a grant from The Fluid Research Fund, Yale Univ School of Medicine*]

**Double discharges in human motor units** J S DENSLOW (introduced by Irvin M Korr) *Still Memorial Research Trust, Kirksville, Mo* Electromyograms of single motor units indicate that the temporal and voltage pattern of a given unit remains reasonably constant and characteristic when the electrode placement remains unchanged Complex patterns which permit definite identification are best recorded with an enameled needle, bare at the tip, and paired with an intradermal needle in a nearby inactive area

Double discharges of single units, identified by their patterns, were recorded in the human trapezius muscle Similar double beats occurred rarely, if ever, in the biceps and triceps muscles Single units were activated by mild, steady, voluntary contraction or, in addition, in the trapezius, by light pin scratches on the skin at some distance from the electrode Abrupt voluntary twitches were carefully avoided

The double beats have the following characteristics (a) the time interval between the two beats ranges from 3 to 20 msec although "couples" at intervals greater than 20 msec are seen, (b) they usually occur as the unit starts, occasionally as it stops and, at times, are interspersed with single

beats, (c) long strings of doubles often continue after a skin stimulus is withdrawn and in the absence of surges of voluntary effort, (d) the time interval between two beats varies in a series of doubles (e) Double discharges have lower frequency limits than singles

The relation of doubling to supernormality and subnormality at the soma of the motoneuron suggested by Hoff and Grant (*J Neurophysiol* 7 305, 1944) is discussed

**Velocity of arm flexions under varying loads** R F DERN (introduced by W O Fenn) *Dept of Physiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, N Y* In an isolated muscle contracting against different loads, the velocity of shortening diminishes as the load increases Various equations have been applied to this curve by A V Hill and others Our experiments were designed to discover whether similar laws governed the speeds of shortening of human arm muscles contracting against different constant loads or different inertias While under some conditions, a typical force-velocity curve can be obtained, with other techniques some subjects develop a constant moment of force (torque) around the elbow joint, over a wide range of different velocities of flexion In the latter case, the force in the muscle, itself, must be progressively diminishing in proportion to the increase in the effective lever arm, but, in any contraction, must be largely independent of the velocity of shortening This suggests that the speed of movement in human limbs is limited to a large extent by the amount of innervation delivered to the muscle rather than by the fundamental properties of the contractile mechanism itself Furthermore electromyographic studies indicate considerable activity of the antagonistic muscles throughout the single contraction and suggest that the amount of such activity may vary with the magnitude of the load opposing the movement This would still further complicate any interpretation of the dynamics of human arm movement in terms of laws derived from isolated muscles

**The effect of posture on the creatinine clearance of unanesthetized dogs** INGRITH J DEYRUP (introduced by Magnus I Gregersen) *Dept of Physiology, College of Physicians and Surgeons, Columbia Univ* Repeated creatinine clearance determinations were carried out on trained unanesthetized dogs to evaluate the effect of body position on glomerular filtration rate The dogs were either placed in the supine position on a comfortable animal board, or were partially supported in the upright position in a modified Pavlov stand Creatinine was administered by subcutaneous and intravenous injection In some experiments the rate of urine flow was at the low basal level (8 to

31 ml per hour) while in other tests the animals were given 25 ml water per kgm and determinations were carried out during the subsequent water diuresis. Observations were continued over a period of 2.5 hours.

In the standing position the creatinine clearance tended to fall progressively after the first hour of observation. At the end of 2.5 hours the clearance usually ranged from 50 to 80 per cent of the initial value. In contrast to this finding, no consistent change in creatinine clearance occurred in the supine position. Usually the clearance varied within  $\pm 10$  per cent of the initial value throughout the period of observation. There was no consistent difference in the pattern of urine flow and plasma proteins (refractometric method) and relative red cell volumes were essentially constant in both standing and supine positions.

The mechanism of the slow progressive fall in creatinine clearance observed in the standing but not in the supine position is not at present understood.

**Endocrine influences on muscle strength and neuromuscular atrophy and regeneration.** R. DIAZ GUERRINO and I. D. INOYSON (introduced by H. M. Hines) *Dept. of Physiology, State Univ. of Iowa, Iowa City.* These studies were made on the gastrocnemius muscle and tibial nerves of hyperthyroid, hypothyroid, thyrectomized and castrated adult albino rats and matched normal controls. The state of hypothyroidism was produced by thiouracil administration and hyperthyroidism by thyroxin administration. The tibial nerve of one limb was crushed in such a way as to produce complete denervation of the gastrocnemius muscle. The non-denervated contralateral limb served as a control. Measurements of muscle weight and strength were made at various times after denervation. The strength of the muscle was determined by measuring the amount of isometric tension which developed in response to direct and nerve stimulation.

Thyrectomy and castration had no appreciable effects upon either the strength of non-denervated muscles or upon the rate and extent of neuromuscular regeneration following denervation. The initial signs of functional reinnervation appeared slightly earlier in the hyperthyroid animals than in normal and hypothyroid animals. Thyroxin administration increased and thiouracil administration decreased the rate of atrophy which occurred in the gastrocnemius muscles following denervation. Studies made on the animals at various times during neuromuscular regeneration indicated that *functional reinnervation was slower in hypothyroid than in hyperthyroid animals.* The results of the experiments showed that the effects of thyroxin administration were to decrease and the effects of

thiouracil were to increase the capacity of normally innervated muscle to develop tension.

**Contracture and suppression of cortical activity.** C. F. DICK (by invitation), J. F. BOSMA (by invitation), and L. GILHOUS *Laby of Neuropsychology, Univ. of Minnesota.* Experiments were performed on "Dial" cats in which a contracture of the gastrocnemius and other muscles of the hind limb was induced by tenotomy or electrical stimulation of the sciatic nerve. It was found that stretching these muscles elicited delayed and often repetitive suppression of the motor cortex as indicated by the magnitude of the movement resulting from stimulation of the motor cortex with a standardized electrical stimulus. As in the experiments of Dusser de Barenne and McCulloch in which the cortical suppressor areas were stimulated electrically the suppressor effect started usually after a latent period of 4 to 10 minutes. It lasted in our experiments for 3 to 6 minutes and frequently appeared again for a similar period.

The analysis of the EMG's accompanying the cortically induced movements showed not only that they were reduced quantitatively, but also that the summation time was greatly lengthened as a result of stretching the contracted muscle. Moreover, co-innervation, i.e. activity of agonist and antagonist was replaced by contraction of the agonist alone and was preceded and followed by inhibition. In control experiments similar changes resulting from the diminution of the intensity or of the duration of the cortical stimulation were interpreted as due to the activation of a lesser number of cortical neurons (Bosma and Gellhorn, 1946). It is therefore suggested that afferent impulses originating in contracted muscles under stretch activate cortical suppressor areas and thereby reduce the number of neurons of the motor area which respond to the standard stimulus. [Aided by a grant from the National Foundation for Infantile Paralysis.]

**Experimental diabetes mellitus produced by intraperitoneal injections of glucose.** F. C. DOHAN, and F. D. W. LUKENS *George S. Cox Medical Research Inst., Univ. of Pennsylvania.* The possible role of hyperglycemia in the production of lesions of the islands of Langerhans and permanent diabetes has been further studied as follows. Twenty per cent glucose in physiological saline was injected intraperitoneally into cats at approximately 8 hour intervals in amounts totaling 150-420 ml per day. Vitamins, especially thiamine, were given in large amounts. The amounts of meat eaten and urine glucose excreted were determined daily. Some cats died after a few days with a syndrome of anorexia, ataxia and weakness but others tolerated the injections for weeks.

Three cats, one normal and two with half the pancreas removed, remained permanently diabetic

after stopping the administration of glucose. Permanent diabetes occurred after 38 to 55 days of glucose treatment, a period similar to that required to produce pituitary-diabetes.

Seven cats, injected for 14 to 104 days, had hyperglycemia for 9 or more days and at autopsy showed marked hydropic degeneration of the islands of Langerhans. For the 3 days before autopsy these animals excreted 66-107% (average 88%) of the available carbohydrate intake. In contrast, 13 cats, injected for 5 to 24 days and showing hyperglycemia on eight days or less, had no hydropic degeneration. They excreted 8-75% (average 39%) of the available carbohydrate prior to autopsy.

Thus, hydropic degeneration of the islets and permanent diabetes mellitus have followed prolonged hyperglycemia produced by glucose injections. Other disturbances than hyperglycemia which may be responsible for the island lesions are being sought.

**Binding of Brilliant Vital Red and T-1824 by serum albumin comparative spectrophotometric studies.** PHILIP DOW *Dept of Physiology, Univ of Georgia School of Medicine, Augusta, Georgia*. As previously reported in these abstracts (1945), attempts are being made to reconcile the extensive but conflicting evidence about the physiological and analytical behavior of Brilliant Vital Red and T-1824 in plasma. The data reported consist chiefly of spectrophotometric studies of practically salt-free solutions of the two dyes in water, in ethyl alcohol, and in a wide range of concentrations of crystallized bovine serum albumin (generously supplied by the Armour Laboratories).

Many of the curves were obtained with a spectrophotometer whose construction is described elsewhere (*Am Jour Physiol* Nov, 1946). The recent availability of a Beckman Model DU (provided by a grant from the U S Public Health Service to the Department of Medicine) has permitted extension of the studies into the ultraviolet spectrum.

Characteristic constants for the reactions between the albumin and the dyes have been estimated. Their significance, however, is weakened by Rawson's (1942) evidence for the existence of different protein dye combinations at low and at high albumin concentrations. The present data support Rawson's conclusions and suggest that redistribution of dye molecules may begin even before the initial binding (at high dye:albumin ratios) is complete. The spectrophotometric method emphasizes this caution in interpretation, since the sole presence of the intermediate compound is difficult to confirm by the study of the absorption spectra.

A possible correlate of the differences in precipitability of the two dyes combined with albumin is found in the contrasting deviations of the curves for alcohol and water solutions of the dyes.

**The relative importance of nervous and humoral factors in gastric secretion.** LESTER R. DRAGSTEDT, E. BRUCE TOVEE (by invitation), EDWARD R. WOODWARD (by invitation), and PAUL V. HARPER (by invitation). *Dept of Surgery of The Univ of Chicago*. Observations have been made on the continuous secretion of gastric juice in the empty stomachs of 160 patients with various types of peptic ulcer both before and after section of the vagus nerves to the stomach. An abnormally large secretion occurs in most ulcer patients and this is reduced to normal values by vagus section thus indicating that it is neurogenic in origin.

The gastric secretion of dogs may be collected quantitatively in animals prepared with a completely isolated stomach with blood supply and vagus innervation preserved as described by Dragstedt and Ellis (*Dragstedt, L. R., and Ellis, J. C., Am Jour Physiol* 93:407, 1930). Subsequent section of the vagus nerves in these animals reduces the secretion of gastric juice to 10 to 20 per cent of the initial level.

In both man and the dog, nervous factors are far more important than all other influences combined in determining the volume and acidity of the gastric juice.

**Influence of thyroid gland on the conversion of carotene to vitamin A.** VICTOR A. DRILL and ALDO P. TRUANT (by invitation). *From the Dept of Pharmacology and Toxicology, Yale Univ School of Medicine, New Haven, Connecticut*. Normal thyroidectomized rats, weighing between 40 and 50 grams, were fed a vitamin A free diet. Supplements of 5 gamma of vitamin A or 10 gamma of carotene, injected subcutaneously every 2 days, allowed a comparable gain in weight and prevented ocular lesions in the unoperated rats. When similar vitamin supplements were administered to the thyroidectomized rats the vitamin A prevented the appearance of xerophthalmia, but the carotene failed to prevent the ocular lesions of vitamin A deficiency. The vitamin A treated thyroidectomized animals showed a slight gain in weight. The carotene-treated thyroidectomized animals did not gain weight for the first 45 days of the experiment, and showed a weight curve similar to that of thyroidectomized control animals not receiving vitamin A or carotene.

The failure of the thyroidectomized animals to utilize carotene was not complete for, although the mortality was high, some animals survived longer than untreated control animals. Those that survived past the 45th day also showed a slight gain in weight during the next 39 days, although, their ophthalmic lesions did not regress during this period. It is evident that the thyroid gland plays a major role in the conversion of carotene to vitamin A. [Work aided by a grant from the Fluid Research Fund, Yale University.]

Absorption from the pulmonary alveoli CECIL K. DRINKER and ESTHER HARDENBERG (by invitation) *Dept of Physiology, Harvard School of Public Health* Dogs anesthetized with Nembutal have been prepared for observation by cannulation of the trachea, cannulation of a femoral artery and vein, and cannulation of the thoracic and right lymphatic ducts. Lymph from the lungs does not flow into the thoracic duct except in rare cases and can be collected from the right lymphatic duct, if precautions are taken to ascertain that this lymph is not mixed with thoracic duct lymph, which occurs in about 50 per cent of the cases.

Using care to be assured that uncontaminated right duct lymph was being collected, the authors instilled intratracheally solutions of dog plasma, purified bovine serum albumin, purified egg albumin, hemoglobin, and a suspension of glass spheres averaging  $4\mu$  in diameter.

The conclusions reached were that with normal alveolar epithelium none of these foreign substances reached blood or lymph except very slowly and in traces. In order to achieve substantial absorption of proteins from the alveoli, enzymatic action is apparently necessary with breakdown into molecules diffusing readily through the pulmonary epithelium. In the case of the foreign particles used, though intralveolar phagocytosis was observed, there was no evidence of entrance into the lymph stream during 4 hours of observation.

Rectangular pulse generator for stimulating tissue A. L. DUNN (by invitation) and A. R. McINTIRE *Dept of Physiology and Pharmacology, Univ of Nebraska, College of Medicine, Omaha* A rectangular pulse generator has been constructed which supplies positive pulses of continuously variable amplitude from zero to thirty volts, continuously variable frequency from one cycle to five hundred cycles per second, and continuously variable duration from  $\frac{1}{2 \times \text{frequency}}$  second to  $\frac{1}{2 \times \text{frequency}}$  second.

A negative pulse can be introduced to alternate with the positive pulse. Its amplitude and duration are continuously variable, its frequency is the same as that of the positive pulse. A monophasic and a biphasic spike shock can also be produced. The wave form of the stimulus applied to the tissue is observed by means of a cathode ray oscilloscope.

The effect of different grades of penicillin on the motility of the rabbit uterus ABRAHAM DURY (by invitation), EUGENE D. ROBIN (by invitation) and CHESTER E. LEESE *Dept of Physiology, George Washington Univ Medical School* The effect of the three grades of penicillin on the estrus rabbit uterus was tested. The least pure product (Calcium penicillin—Winthrop) had an approximate potency of 350 Oxford units per mgm. The next purer product (Calcium penicillin—Squibb) had an ap-

proximate potency of 1000 Oxford units per mgm. The purest product tested was Crystalline Penicillin K with a potency of 1625 units per mgm. Kymograph records of the estrus rabbit with a chronic uterine fistula were observed following intramuscular injections of each of these penicillin products.

Rabbits with intra muscular injection of 50,000 units of low potency penicillin (Ca—Winthrop) showed approximately two hours of abnormal uterine activity. This consisted of extended periods of no contraction, or contractions of very small amplitude alternating with occasional periods of greater than normal contractions.

Rabbits with intra-muscular injection of 50,000 units of commercial penicillin (Ca—Squibb) showed an increase in uterine tone concomitant with a decrease in the rate and the amplitude of contractions. Injection of an additional 50,000 units of this grade of penicillin accentuated the effect on the uterine motility resulting in an extended state of no contractions. The cumulative effect of the 100,000 units of this penicillin approximated the effect of 50,000 units of the low potency penicillin.

Intra muscular injections of crystalline penicillin K in large quantities (120,000 Oxford units) showed no effect upon the motility of the rabbit uterus.

The above experiments suggest that the effect of penicillin upon the motility of the estrus rabbit uterus is due to an impurity present in the two grades of non crystalline penicillin.

Alloxan diabetes in the sheep J. A. DYE and BARBARA A. WOODWARD (by invitation) *Dept of Physiology, Cornell Univ, Ithaca* Diabetes was produced in two young Hampshire ewes by intravenous injection of alloxan, 116 and 93 mg per kg in sheep 1 and 2, respectively. In each the response was typically triphasic: initial hyperglycemia, secondary hypoglycemia, and subsequent maintained hyperglycemia. Although hypoglycemia of 14 and 26 mg per 100 ml were reached, convulsions and coma were absent.

Sheep 1 later developed hyperpnea, weakness, prostration, anuria with retention of nitrogen and glucose, and coma, and died 85 hours postinjection. Diuretics were ineffective. The terminal gly cemia was 665 mg per 100 ml, blood non-protein nitrogen 167 mg per 100 ml, while ketonemia was insignificant.

Kidney damage was slight in sheep 2, anuria was absent. The glycemia in this animal varied from 202 to 264 mg per 100 ml with normal diet, but fell to 182 mg per 100 ml during a seven day fast. The daily urinary glucose excretion was as low as 3 grams during fasting, but ranged from 77 to 148 grams with feeding. Polyuria and polyphagia prevailed. The single intravenous glucose tolerance test performed was normal. An insignificant initial

rise of blood non-protein nitrogen occurred, thereafter, normal values were obtained. After two months' survival, this animal developed weakness, lethargy, and prostration, the glycemia was 202 mg per 100 ml, ketosis was present but mild. Insulin administration revived the animal. On the tenth day of this treatment, a hypoglycemia of 8 mg per 100 ml with coma developed, convulsions were absent. Glucose administration failed to restore her to normal.

**The oxygen metabolism of the dog's heart**  
JAMES E. ECKENHOFF, JOSEPH H. HAFKENSCHIEL, CHARLES M. LANDMESSER, and MEREL H. HARMEL (introduced by Carl F. Schmidt) *Dept of Pharmacology and Harrison Dept of Surgical Research, Univ of Pennsylvania, and Dept of Anesthesiology, Hospital of the Univ of Pennsylvania, Philadelphia*. In spontaneously breathing dogs, lightly anesthetized with nembutal, coronary blood flow was measured by the use of the bubble flowmeter. Coronary venous blood was collected directly from the great cardiac vein. From the curves representing the uptake of nitrous oxide during the inhalation of that gas, we concluded that this was uncontaminated coronary venous blood whereas samples collected from the coronary sinus were not. Left ventricular oxygen consumption was determined by the product of the A-V (coronary) oxygen difference and the coronary blood flow per 100 grams of left ventricle per minute.

The oxygen content of "normal" coronary venous blood under the conditions of these experiments was 4-6 volumes per cent when right ventricular blood contained 12-16 and arterial blood 19-21 volumes per cent. This figure was consistent and was proven not to be due to venous stasis nor solely or largely to the anesthetic agents used.

Under the conditions of these experiments the mean oxygen consumption of the left ventricle was 8.8 cc per 100 grams of left ventricle per minute (S.D.  $\pm 1.1$ ).

Cardiac oxygen consumption showed an excellent correlation with coronary blood flow ( $r = 0.85$ ). Since coronary blood flow is closely related with arterial blood pressure, a correspondingly good correlation exists between the latter and cardiac oxygen consumption ( $r = 0.67$ ).

Between cardiac oxygen consumption and coronary resistance (expressed as coronary flow per 100 grams per minute over mean arterial blood pressure) the relationship was fair ( $r = 0.63$ ). Between cardiac oxygen consumption and cardiac work the relationship was poorer ( $r = 0.50$ ), other factors obviously being present. The correlation with cardiac output was poor ( $r = 0.09$ ).

**The effect of explosive decompression to 30 mm Hg on the lung volume of the rat** ABRAHAM EDELMAN and R. W. STACY (introduced by Fred A. Hitchcock) *Dept of Physiology, Ohio State*

*Univ, Columbus*. A method has been devised for the determination of the volume of air in the lungs. It consists of measuring the volume of normal saline displaced by the lungs, then reducing the ambient pressure to 500 mm Hg and measuring the amount of expansion which occurs (the pressure-volume relationship is a straight line for the pressure changes used), and calculating the volume of air by an application of Boyle's Law. Such determinations have been made on the lungs of rats before and after collapse. The results on 10 normal 150 gram rats are as follows: lung weight, 1.03 grams, lung volume before collapse, 1.70 cc, after collapse, 1.36, air in lungs before collapse, 0.79, after collapse, 0.47 cc. The calculated specific gravity of the lungs is 0.61 before collapse and 0.75 after collapse.

This method is being used as a means of estimating the amount of lung damage resulting from explosive decompression to 30 mm Hg. Results indicate that explosive decompression daily for five days produces a significant decrease in the volume of air in the lungs, which probably is due to atelectasis since there is no increase in lung weight. Rats explosively decompressed daily for fewer than five days show no significant change in lung volume. Rats that have been explosively decompressed five times in rapid succession also show a decrease in the air contained in the lungs, but since there is an increase in lung weight, this change would seem to be due to hemorrhage.

**The sphincter of Oddi** M. EISENSTEIN (by invitation) and H. NECHELES *Dept of Gastro-Intestinal Research, Michael Reese Hospital, Chicago*. In anesthetized dogs physiological saline solution was perfused through the common duct and the sphincter of Oddi into the duodenum. The perfusion pressure was registered. A constant intravenous injection of prostigmine increased perfusion pressure considerably. Following suitable control periods, solutions of drugs with topic anesthetic effects were substituted for the saline perfusate of the common duct. The resistance to perfusion dropped markedly for considerable periods of time. The intravenous injection of the same dose of the same topic anesthetic drug did not relax the sphincter of Oddi as much nor for as long a period of time than when perfused through the common duct.

Some of the topic anesthetic drugs employed, such as trasentin, are used in medicine as spasmolytic drugs. It seems that part of the effect of such drugs are due to local interruption of reflexes rather than to systemic antispasmodic action.

**The distinction between alveolar and ventilatory types of pulmonary dysfunction** JAMES O. ELAM (by invitation), A. HEMINGWAY and M. B. VISSCHER *Dept of Physiology, Univ of Minnesota Medical School, Minneapolis*. Patients with acute pneumonitis were studied with the Millikan

Smaller oximeter and by  $V$  in Shike arterial oxygen saturation determinations. In cases with brain stem dysfunction, the so called bulbar forms of the disease, there may be normal minute respiratory volumes but nevertheless a low arterial oxygen saturation while breathing room air. Increasing pulmonary ventilation has little if any effect upon the arterial oxygen saturation. Upon oxygen administration, however, the arterial oxygen saturation rises slowly to values which sometimes approach 100 per cent. Patients responding in this way are found to suffer from pulmonary edema, atelectasis and/or hemorrhage. In patients with paralysis of respiratory muscles, the spinal form, increase in the tidal exchange with room air by artificial respiration raises the arterial oxygen saturation to about 95 per cent and oxygen administration brings about the same rise found in normal subjects, to 100 per cent. The difference in responses of the two types of patients distinguishes between primary alveolar and primary ventilatory defects in the respiratory mechanism.

The effect of prostigmine methylsulphate on the pelvic symphysis of the guinea-pig. FREDERICK E. LAURIA and ALFRED H. LAWTON (by invitation) *Dept. of Physiology and Pharmacology, Univ. of Arkansas*. A few months ago a group of guinea-pigs injected with progesterone and desoxycorticosterone acetate were being studied for relaxation of the pubic symphysis. In some of them the separation of the pubic bones could scarcely be detected while in many animals the pelvis was similar to that of advanced pregnancy. This observation led to a search for something that would enhance the reaction. The first substance tried was prostigmine. It proved to be very successful not only in guinea-pigs after injections of theelin and progesterone, but also when given alone.

Considerable relaxation of the symphysis was also induced by one milligram of theelin followed in a few days by one tenth milligram of prostigmine.

Even if prostigmine was injected three or more weeks after the estrogen, marked separation of the pubic bones often occurred. Oophorectomy seems to aid the response.

The adrenal cortex and urea synthesis in the nephrectomized rat. FRANK L. ENGEL, E. IRENE PEVZT, and MILDRED G. ENCL (introduced by Eugene A. Stead Jr.), with the Technical Assistance of M. Standifer. *Dept. of Medicine, Emory Univ. School of Medicine, Atlanta, Ga.* A sensitive method for the measurement of urea production during brief time intervals has been devised, using rats 16-17 hours after nephrectomy. Total urea synthesis was calculated from blood urea levels on the basis of the equal distribution of urea throughout the body water, i.e. 75 per cent of the body weight. Male Sprague Dawley rats, red Rockland

rat chow until nephrectomy, were found to produce urea at a constant rate during the first 22 hours after nephrectomy, measurements being made from 0-16 hours, 16-19 hours and 19-22 hours, and sometimes 22-46 hours after nephrectomy. Intravenous administration of a mixture of the 10 essential amino acids plus glycine (Merck's Vuy) at a dose of 8.1 mg N/100 grams body weight at the 19th hour resulted in the conversion of approximately 50 per cent of the injected nitrogen into urea during the subsequent 3 hours. Subcutaneous injection of 0.2 ml /100 grams body weight of Upjohn's aqueous cortical extract at the 16th and 17th hours had no effect on subsequent urea synthesis in otherwise untreated nephrectomized rats. Double this dose promoted synthesis of an additional 4.38 mg urea N/100 grams body weight during the 3rd to 6th hours after injection. When given in conjunction with intravenous amino acids, cortical hormone, even at a dose of 0.6 ml /100 grams body weight at the 16th and 17th hours effected no greater synthesis of urea during the 3rd to 6th hours after injection than did either the amino acids or the cortical extract alone. The significance of these findings with respect to the relation of the adrenal cortex to nitrogen metabolism will be considered. (Aided by a grant from the Committee on Research in Endocrinology of the National Research Council.)

The effect of d-tubocurarine on the central nervous system. G. M. EVERETT (introduced by R. A. Richards) *Dept. of Pharmacology, Abbott Labs., North Chicago, Illinois*. In a series of studies on cats, rabbits and rats either prepared with epidural electrodes or silver electrodes on exposed cortex the effect of d-tubocurarine on the EEG, the spike response to stimulation of contralateral cortex, and the induction of convulsive activity by electro shock or metrazol were determined. Great care is necessary in such studies to insure adequate artificial respiration. Usually high  $O_2$  was added. No signs of convulsions or twitching were observed unless anoxia was allowed to develop. The curarizing dose sufficient to cause respiratory paralysis in all these species is approximately 0.2 mg/kg d-tubocurarine. With doses from 5 to 50 times this amount no effect on the EEG was noted. Further, the convulsive dose of metrazol produced a typical firing off of the cortex although all motor manifestations were absent and the electromyograph showed no spikes.

In these studies it would appear that d-tubocurarine had little or no direct effect on the CNS. It seems probable that previous reports by others of a convulsant action of d-tubocurarine were due to inadequate artificial respiration and subsequent anoxic phenomena.

Electrical characteristics of cardiac muscle injuries. J. A. C. EXETER and W. E. GIBSON (by invitation) *Dept. of Physiology, Univ. of Wisconsin*.

sin Medical School, Madison Local regions of injury were produced on the ventricles of snapping turtles and dogs by the use of suction electrodes connected through direct coupled amplifiers and cathode ray oscillographs. Potential, current flow and impedance were determined. On placing various values of resistance in parallel with the injuries ("loading resistances"), it was found that the current flow increased from about 60 microamperes to about 105 microamperes with decrease of the parallel resistance from 5000 ohms to 1000 ohms. Resistance of lower value down to 100 ohms caused no greater current flow. The impedance on the other hand rose steadily with lower parallel resistances down to 100 ohms from a value of about 2,700 to 4,200 ohms.

Comparison of the electronegative and electropositive phases of the injury showed that the latter was associated with higher potential development, greater current flow and lower impedance. Increasing the area exposed to injury resulted in no significant change in voltage but significant increase in current flow and lowered impedance. Comparing two injuries separately and in parallel showed no significant changes in potential, but significant increase in current flow and decrease in impedance with the injuries in parallel.

It is concluded that an injured region is the source of electric energy that has the characteristics of an electromotive cell or battery.

**Tryptase (plasmin) and blood coagulation** J H FERGUSON, B L TRAVIS (by invitation), and E B GERHEIM (by invitation) *Dept of Physiology, Univ of North Carolina, Chapel Hill* Natural protease (tryptase or plasmin or fibrinolytic enzyme), studied in a variety of modern plasma protein products, resembles weak pancreatic trypsin in 1 many proteolytic actions, incl fibrinolysis, fibrinogenolysis, etc and 2 "thromboplastic" activation of prothrombin to thrombin. All these actions are inhibited by trypsin-inhibitors from pancreas, soy-bean, and egg-white. Heparin, in amounts which are slightly antithrombic, does not prevent the activation or the actions of tryptase. The plasma enzyme exists as an inactive precursor (tryptogen), absent from certain plasma products. Other fractions, however, contain tryptogen or tryptase or both. Enzyme activation is best obtained by suitable kinase, e.g. streptokinase (mis-called "streptococcal fibrinolysin"). Streptokinase, itself, is devoid of proteolytic, thrombic, or thromboplastic effects. In showing up the thromboplastic action of tryptase (cf. trypsin) on highly purified prothrombin, it is important to use amounts of enzyme too small to give interfering proteolytic (oporthrombinolytic) effects.

**Control of peripheral blood flow responses in the human hand when other extremities are warmed** B G FERRIS, Jr, R E FORSTER, II,

E L PILLION, and W R CHRISTENSEN (introduced by H S Belding) *The Quartermaster Corps, Climatic Research Lab, Lawrence, Mass* The blood flows and skin temperatures of both hands of two lightly clad, male subjects were studied at ambient temperatures ranging from 16° to 30°C, using air plethysmographs and thermocouples. Before recording blood flows, subjects were exposed to a particular ambient temperature until a steady state was attained.

At an ambient temperature of 17°C, heating one hand to a skin temperature as high as 42.1°C had no effect on skin temperature or blood flow in the opposite hand, but did increase blood flow in the heated hand slightly above the control value. Needle thermocouple studies revealed thorough warming of the heated hand, and marked cooling of the unheated hand. With both legs immersed in a water bath at 42°C, an increase in hand blood flow and skin temperature occurred. Baths at 40° and 38°C produced no such effects.

At an ambient temperature of 22°C, an increase in blood flow occurred in the heated hand only. However, at 24°C, both hands revealed increased blood flows and skin temperatures. At 30°C, only the heated hand demonstrated any alteration in blood flow.

It is concluded that, under "cold" ambient conditions (21.5°C or lower), unless considerable heat is applied, pronounced vasoconstriction, probably centrally-mediated, prohibits local or generalized vasodilatation. In the higher temperature range, body heat-loss is not so rapid, and merely warming one hand is enough to cause vasodilatation at 24°C, at 30°C, marked vasodilatation has occurred and any further heat load is dissipated largely by an increase in evaporation.

**Effect of sodium caprylate on the thermal stability of the respiratory system in rat brain** JOHN FIELD 2ND and RUTH L DRYER (by invitation) *Dept of Physiology, Stanford Univ* Low concentrations of sodium caprylate and related compounds markedly increase the thermal stability of human and bovine serum albumin (Ballou, Boyer, Luck and Lum, 1944). Furthermore, caprylate inhibits the denaturation of albumin by urea or guanidine (Boyer, 1945). The present experiments were undertaken to determine whether caprylate would increase the thermal stability of the respiratory system of rat cerebral cortex, which is presumably conditioned by the properties of the protein components of the several enzymes.

To this end the oxygen consumption ( $Q_{O_2}$ ) of rat cerebral cortex slices (hereafter "brain slices") was measured by the Warburg method in the presence of graded concentrations of sodium caprylate. Concentrations ranging from  $1 \times 10^{-7}$  M to  $1 \times 10^{-3}$  M did not affect brain slice  $Q_{O_2}$  at 37.5°C for periods up to 3 hours. However, in the



presence of certain concentrations of caprylate, brain slice QO<sub>2</sub> decreased more rapidly after 10 minutes at 15°C or 70 minutes at 12.5°C followed by transfer to 37.5° than in similarly treated controls. The lowest tested concentrations of caprylate which produced this effect were  $1 \times 10^{-5}$  M at 45°C and  $1 \times 10^{-4}$  M at 42.5°C. Thus, under the conditions of these experiments, sodium caprylate lessened rather than increased the capacity of the respiratory system of cerebral cortex slices to withstand damage by heat.

Potentialation of response of rectus abdominis of frog to acetylcholine by diisopropyl fluorophosphate. JOHN C. FINEY (introduced by Robert Gesell). *Physiology Lab., Univ. of Michigan, Ann Arbor*. Solutions of diisopropyl fluorophosphate (DFP) which produced a marked increase in the response of isolated skeletal muscles to exogenous acetylcholine were acid in character. Determinations of the acidity of a bicarbonate free Ringer Locke solution containing M/2500 DFP indicated a pH of 3.3.

Adjustment of DFP solutions to a pH value of approximately 7.0 by the addition of sodium bicarbonate produced a marked reduction of potentiation.

The potentiation produced by unbuffered solution of DFP could, therefore, be a combined effect of the anticholinesterase activity of pH and DFP. This is supported by a comparison of the effects of several acids on the response of the rectus abdominis to acetylcholine. CO<sub>2</sub>, lactic acid, phosphoric acid and hydrochloric acid produced increased responses to acetylcholine, the extent of which seemed to be related to the penetrating properties of the acid (Jacobs 1920, Finerty and Gesell 1945).

Adenosinetriphosphatase activity of myosin from denervated skeletal muscle. ERNST FISCHER, ERNST HUB (by invitation), and W. RAMSEY (by invitation) and C. R. RYLAND (by invitation). *Baruch Center of Physical Medicine, Medical College of Virginia, Richmond*. Myosin was extracted from mash of normal and denervated rabbit muscles according to the method of Szent Györgyi and purified by repeated precipitation. The adenosine triphosphatase activity per mg protein of the various fractions were tested with dog and rabbit ATP as substrate. For myosin from normal muscle, the increase in ATPase activity with purification is mainly due to removal of proteins without any ATPase activity. The removal of inhibitory impurities is of minor importance and well demonstrable only for the first precipitation.

Crude myosin extracts from denervated muscle have a much lower ATPase activity than those from normal muscle. This decrease is not due to increase in inhibitory substances. With purification, the activity of the myosin increases more

distinctly for denervated than for normal muscle, but the ratio of precipitated protein to non-precipitated is much smaller for myosin from denervated muscles. In contrast to myosin from normal muscle, the non-precipitated fraction of myosin from denervated muscle has some ATPase activity.

The most purified myosin obtainable from muscle denervated for 25 days (weight loss of 40%) had an ATPase activity of about  $\frac{2}{3}$  of normal myosin. Calculations of the total ATPase activity per gram muscle from the ratio and the activities of the various fractions, revealed that during the first week of denervation (weight loss of about 10%), the ATPase activity declines only little but diminishes then rapidly, so that after 25 days (at 40% weight loss) the ATPase activity is only about 15% of that of normal muscle.

Insulin, citrate and the rate of oxygen consumption by isolated intact frog muscle. KENNETH C. FISHER, JAMES HALL (by invitation) and JOSEPH STERN (by invitation). *Univ. of Toronto, Toronto, Canada*. Both insulin and citrate stimulate the rate of oxygen consumption by isolated frog muscle. These effects however are variable from one animal to another, and show marked seasonal fluctuations. Thus in late summer citrate in the concentrations used has little effect, while insulin stimulates. The converse is true in winter animals, i.e. during January and February.

The effect of insulin in the presence of citrate is likewise very variable from one animal to another and the average effect undergoes a marked seasonal fluctuation. On winter animals, i.e. during January and February, insulin added to muscles respiring in the presence of citrate increases the rate of oxygen consumption on the average about 30%, while in the summer there is, on the average, no effect. The effect can be increased, at certain times of the year, by injecting organisms prior to the removal of the muscles, with macerated frog pituitary gland or by subjecting the animals to abnormal warmth. It is found to be related, under all circumstances to the glycogen content of the muscles.

It is a pleasure to acknowledge that this research was made possible, in large part, by grants from The Banting Foundation of Toronto.

Determination of gases in 0.7 to 0.14 cubic millimeter of blood.<sup>1</sup> WALTER FLAGG (introduced by Laurence Irving). *Edward Martin Biological Lab., Swarthmore College*. The method permits sampling, transfer and determination of carbon dioxide and oxygen in 0.7 to 0.14 cubic millimeter

<sup>1</sup> This work was done with the aid of Cost Reimbursement Scientific Research and Development Contract #W33-038 ac-14378 between Swarthmore College (Department of Zoology) and the Air Materiel Command Wright Field.



blood with an accuracy of  $\pm 0.6$  per cent for the larger and  $\pm 1$  per cent for the smaller samples

The blood is sampled into a fine glass capillary and transferred directly to a mercury filled micrometer burette of one cubic millimeter capacity accurate to approximately one in 3000. Between the burette needle and the micrometer is interposed a mercury filled detachable extraction chamber which on its walls has a coating of dried acid and ferrieyanide. The tip of the needle, containing the blood sample, is capped off with wax and the needle-extraction chamber unit detached from the micrometer and placed in a centrifuge tube with the lower end of the extraction chamber dipping into the mercury. Vacuum extraction and mixing of the sample with the dried reagents takes place by centrifugation. Reabsorption of the extracted blood gases is prevented by sudden stopping of the centrifuge whereby the mercury shoots past the solution sticking to the walls, leaving the extracted gas in contact only with mercury. The burette needle is detached from the extraction tube and put on to the micrometer burette. The wax tip is removed in a drop of acid solution and the gases are analyzed according to the method outlined by Bodil Schmidt Nielsen, "Accurate Analysis of 0.4-0.1 Cubic Millimeter of Gas."

Estimation of carbon dioxide and oxygen in a 12 cubic millimeter blood sample.<sup>1</sup> SARAH C. FLEMISTER (introduced by Laurence Irving) *Edward Martin Biological Lab., Swarthmore College*. The syringe method of Scholander and Roughton for the determination of blood gases has been adapted to the combined estimation of oxygen and carbon dioxide in a 12 cubic millimeter blood sample. The blood sample is laked in the syringe with ferrieyanide saponin solution which releases oxygen from its chemical combination. Strong acid phosphate solution is then introduced to set free the carbon dioxide. The gases are extracted from the solution by vacuum extraction in the syringe. The capillary is cleared and bubbles broken up by whirling the syringe in a simple hand sling. The extracted gases are measured and selectively absorbed by alkali and pyrogallol. The method has been checked against the Van Slyke method and gives accuracies of  $\pm 0.7$  volume per cent for oxygen and  $\pm 1.0$  volume per cent for carbon dioxide on samples of mammalian blood. Analyses indicate that the method is equally accurate for avian and fish blood. The method is useful for work where large blood samples can not be obtained and is well adapted for work in the field.

The response of the pH of synovial fluid in the

anaesthetized dog to circulatory influence FRANK FOLK (by invitation), C. I. REED, and N. R. JOSEPH (by invitation) *Dept. of Physiology and of Medicine, Univ. of Illinois, Chicago Colleges*. Simultaneous observations of the pH of knee joint synovial fluid and femoral venous blood were made on anaesthetized dogs by a method which has been previously reported. Observations in the resting state were compared with those under the following conditions: (1) vagus nerve stimulation, (2) femoral nerve stimulation with resulting muscular contraction, and (3) simultaneous vagus and femoral nerve stimulation. In each case, the pH readings were taken immediately after stimulation and during a recovery period in which the values returned to approximately the resting values. The effect of stimulating the vagus was to lower the blood pH by almost 0.10 on the average, while the joint pH remained unchanged. The blood pH recovered rapidly in the period after stimulation. Femoral nerve stimulation resulted in a lowering of both blood and joint pH, recovering more rapidly in the resting period. Simultaneous femoral and vagus stimulation also resulted in lower pH of both blood and joint, but the effect on blood pH was greater on the average than that on the joint pH. Recovery curves were similar to those in which only the femoral nerve was stimulated. The results indicate that joint pH is not affected by small, transient changes of blood pH, but is influenced markedly by local muscular activity with production of diffusible acid metabolites.

The rate of increase of arterial oxygen saturation following inspiration of 100% oxygen W. S. FOWLER (by invitation) and J. H. COMROE, JR. *Dept. of Physiology and Pharmacology, Graduate School of Medicine, Univ. of Pennsylvania*. Continuous observations were made of the rise in arterial oxygen saturation (oximeter) of normal adults following the change from breathing room air (19 subjects) or low oxygen mixtures (11 subjects) to breathing 100% oxygen. The increase in arterial saturation is initially rapid and then approaches the maximum (100% saturation) more slowly, requiring in both groups an average time of about 45 seconds to reach the maximum. The instrumental lag is about 5 seconds and the circulation lag (lung to ear) 5-10 seconds. Since the first inspiration of 100% oxygen by subjects previously breathing room air raised the  $pO_2$  of the terminal volume of the succeeding expiration ("alveolar" air) to more than 160 mm Hg, at which tension the hemoglobin should be practically completely saturated with oxygen, and since hemoglobin in the lung capillaries is said to become oxygenated in less than a second, there remains about 30 seconds between the attaining of an "alveolar"  $pO_2$  of 160 mm Hg and the appearance of completely saturated arterial blood. One basis for explanation

<sup>1</sup> This work was done with the aid of Cost Reimbursement Scientific Research and Development Contract #W33 035 ac 1492 between Swarthmore College (Department of Zoology) and the Air Materiel Command, Wright Field.

of this time lag may be uneven gas mixing in the lung or slow diffusion, and the rate of arterial oxygen increase may serve as a test of these functions. Hyperventilation with 100% oxygen decreased the time required to reach maximum oxygen saturation. Patients with pulmonary emphysema showed less rapid increases and marked prolongation of time to maximum saturation.

Vasomotor and sudomotor patterns in the skin of the finger and forearm. F. C. FRANK, W. C. RANDALL, D. C. SMITH (by invitation) and A. B. HERTZMAN. *From the Dept of Physiology, St. Louis Univ. School of Medicine, St. Louis, Mo.* The question whether there is a correlation between vasomotor and sudomotor activities in different skin areas has been studied by the simultaneous recording of the cutaneous blood flow and sweating.

We have observed several different combinations of vasoconstriction and sweating in the finger pad and skin of the forearm. Certain patterns of activity are encountered much more frequently than others. Sweating and vasoconstriction in the finger pad are regularly induced by such stimuli as noises, deep inspiration, mental arithmetic, etc. Accompanying vasoconstriction and sweating in the forearm may occur but the absolute magnitude of the change is much less, the relative change in blood flow may be considerable, the relative sweating response is usually much less in the forearm, however, striking changes in both blood flow and sweating have occurred.

Periodic sweating may occur in either the pad or forearm alone or in both simultaneously. Vasoconstrictor waves in the finger are frequently but not always accompanied by similar waves in the forearm, but the absolute magnitude of the changes in the latter tend to mask the smaller waves.

Vasomotor and sudomotor effects in the pad may occur simultaneously without measurable similar changes in the forearm, the converse has not been observed. [Aided by a grant from the United States Public Health Service.]

A method for determining the ulcer-preventive factor in enterogastrone concentrates. JESSE N. FREDERICK (by invitation), and HARRY GREENGARD. *From the Dept of Physiology, Northwestern Univ. Medical School, Chicago, Illinois.* The published methods of bioassay of enterogastrone concentrates are based either on a determination of its ability to depress the parietal secretion of the stomach, or on a test of its effectiveness in preventing ulcer development in the Mann-Williamson dog. The former procedure is brief but indirect, the latter is direct, but requires months to yield its answer. To obviate these defects, the present method has been designed, in which adult white rats are anesthetized, the abdomen opened, and 0.2 to 0.25 cc of 20 per cent phenol in water injected into the stomach wall through the serosa. The

wound is closed and the animals kept for a week, after which they are sacrificed and the injected region of the stomach examined. When assaying the ulcer-preventive potency of an enterogastrone concentrate, this is injected intramuscularly in the rat for six days before and six days after the phenol treatment. The procedure has yielded a definite pouching out of ulcer with an indurated margin in the majority of untreated rats, whereas protection against its development has been noted in most of the injected ones. The advantages of this method of assay lie in its ease of execution, in the relatively short interval required, and in the fact that it measures directly the property of the concentrate which is of primary therapeutic interest.

Spasticity in transverse lesions of the spinal cord in humans. L. W. FREEMAN and R. F. HEIMNURGER (by invitation). *Paraplegia Section, Kennedy Veteran's Administration Hospital, Memphis, Tennessee.* Although careful studies were carried out by Head, Holmes and others on large groups of paraplegic patients in World War I, the survival period in general was too short for accurate appraisal. Intercurrent infections, decubitus ulcers, and renal and vesical calculi, all contributed to a high death rate. Since the advent of newer types of care and chemotherapy, survival has been the rule. This has allowed observations on patients free of complicating features.

Complete transverse lesions of the spinal cord, proven by exploration, are considered separately. Those patients with function below the point of lesion are not included. Physiologically complete lesions which have been present more than one year without change, are discussed. Since the lesions in general were not discrete, the site of injury did not correlate well with the development of spasm. Mass reflexes were not observed, although component parts of the mass reflex were. Crossed extensor thrusts were demonstrated in many instances. Spasm tended to reach its greatest severity in three months, maintained itself at this level for approximately nine months, and then gradually diminished.

Acute and chronic studies in abdominal distention. DAVID M. FRENCH, WALTER M. BOOKER, and PEDRO A. MOLANO (introduced by A. B. Luckhardt). *Dept of Pharmacology, Howard Univ. School of Medicine.* Acute. Previous studies have demonstrated that circulatory failure could be produced in dogs by increasing the intra-abdominal pressure (by inflating a balloon in the peritoneal cavity, the stomach or by air in the peritoneal cavity). Small abdominal areas are apparently more sensitive to a given pressure (5-10 mm. mercury) than larger abdominal areas. Similarly, larger abdominal areas can stand a higher pressure and a longer duration of such pressure before circulatory failure appears than in cases of smaller abdominal

areas, and in animals with smaller abdominal areas there seems to be a tendency toward almost immediate drop in blood pressure upon inflation, while in animals with larger abdominal areas the blood pressure may rise and remain elevated for several minutes or longer, collapsing suddenly. Axis deviation and possible myocardial damage exist, indicated by changes in the contours of the ECG. There is the suggestion that the constriction of coronaries occurs via the vagal pathway, since section of the vagi is followed by a tendency of the ECG to return toward the pre-inflation pattern.

**Chronic Air** was introduced into the peritoneal cavity once or twice a week, increasing the amounts each time in order that there would be a gradual but not too severe increase in abdominal distention. Pressure varied between 10 and 40 mm. of mercury. Some animals succumbed early (2-3 days) to the pressure. Others lasted for weeks or even months with high intraabdominal pressures depending on the care taken in gradually inflating the abdomen (not too severe in early inflations) and on abdominal areas. At death autopsies showed generally hemorrhagic fluid in the abdomen and thorax, hemorrhages over the intestine, hemorrhages over the lungs, distention of the mesenteric vessels, in some instances kidneys and ureters presented picture of hydronephrosis, and in others there were small hemorrhages over the cortical areas of the kidneys. Urinary output decreased following inflation, followed by periods of diuresis. Urinary output returned to normal levels if and when air was allowed to absorb lowering pressure in the abdomen. Mean blood pressure (mercury manometer) is increased slightly or is increased markedly followed by a return just above the pre-inflation levels.

**Cortical connections of parietal and frontal opercula in the monkey (*Macaca Mulatta*)** J D FRENCH, O SUGAR and J CHUSID (introduced by Warren S McCulloch) *From the Depts of Psychiatry and of Neurology and Neurological Surgery, Univ of Illinois College of Medicine, Illinois Neuropsychiatric Inst, Chicago*. By local strychnization and recording induced activity, the connections to and from the infero-parietal and infero-frontal planes (1-p p and 1-f p) and other cortical areas have been mapped. The 1-p p corresponds to Woolsey's secondary sensory receptive area.

The 1-p p has afferent and efferent connections with the pre- and postcentral convolutions bilaterally. The connections are much stronger with the primary sensory cortex than with the primary motor cortex. In general the posterior portion of the 1-p p is connected with the leg and shoulder areas of the sensorimotor cortex and the anterior portion, with the thumb and face areas.

The 1-f p has no connections with the sensorimotor cortex, with possible exception of the face

areas, but projects to area 6 on the neighboring convexity.

The 1-f p and 1-p p are connected across from one hemisphere to the other homotopically. There are no projections from 1-f p of one side to 1-p p of the other side or vice versa.

**Further study of central chemical control of breathing with aid of diisopropylfluorophosphate and prostigmine** JEANNE SISKEL FREY (by invitation) and ROBERT GESELL *Physiology Lab, Univ of Michigan, Ann Arbor*. Initial doses of diisopropylfluorophosphate (DFP) in anesthetized dogs usually produced a slowly increasing hyperpnea and, later, increased activity of accessory respiratory muscles. Effects were more striking when injections were made via the vertebral artery, which suggests importance of central action of DFP. When injections were repeated, torsal respiratory movements often decreased in intensity whereas the intensity of accessory movements continued to increase, which suggests a disturbed balance of nervous integration. Further evidence for a disturbance in balance of nervous control of respiration following DFP was demonstrated by (1) disproportionate potentiation of the expiratory component of eupneic breathing, and (2) a weakened inspiratory component with a relative increase in expiratory component in response to faradic stimulation of the carotid nerve.

Respiratory responses to faradic stimulation of the vagus or carotid nerves during DFP poisoning were followed by prolonged after-discharge not found in control observations.

The effects of prostigmine differed somewhat from those of DFP causing an initial depression of breathing such as described by Schweitzer and Wright. This depression was followed by a progressive increasing hyperventilation. Hyperactivity of respiratory muscles was also noted in animals subjected to uniform artificial ventilation administered to eliminate the anti-cholinesterase effects of decreasing pH during the initial stages of depression.

These experiments complement those of carbon dioxide and physostigmine in supporting the acid neuro-humoral theory of nervous integration of the respiratory act.

**Assay of urinary estrogens by ultraviolet absorption spectrophotometry** HARRY B FRIEDGOOD and JOSEPHINE B GARST (by invitation) *Cancer Research Foundation of California and William G Kerckhoff Labs of Biological Science, California Inst of Technology, Pasadena, California*. Previous studies have demonstrated that ultraviolet absorption spectrophotometry can be applied to the quantitative determination of pooled or single samples of crystalline estrone, estradiol and estriol by virtue of the type of absorption curves and concentration-extinction relations which these hor-

mones exhibit under controlled experimental conditions. Further investigations with this quantitative technique have disclosed that current chemical methods do not effect a clean cut separation of the androgens from the estrogens or of estrinol from the estrone-estradiol fraction. The significant losses of estrogens involved in these manipulations have been difficult, if not impossible, to estimate accurately because of the relative lack of sensitivity of the colorimetric and bioassay methods of quantitation as compared with that of ultraviolet absorption spectrophotometry. On the basis of these findings a new method has been developed for the accurate separation and assay of the three estrogens in aqueous alcoholic solution. A study has been made of the factors involved in the application of ultraviolet absorption spectrophotometry to the extraction and separation of the estrogens from urine—with particular reference to the removal of the background material which interferes with the quantitative reading of the estrogen curves.

Pancreatic secretion in man in response to administration of secretin and insulin. M. H. F. FRIEDMAN and Wm. I. SWARE (by invitation). *Dept. of Physiology, Jefferson Medical College, Philadelphia, Pennsylvania*

Pancreatic secretion in response to secretin administration was studied in 35 healthy subjects and 14 patients suspected of having pancreatic or biliary tract disease. Gastric and duodenal contents were obtained by double lumen tube with continuous aspiration. The secretin was prepared by a procedure developed in this laboratory (Friedman and Thomas) and was found free from toxic effects.

In one series of 26 healthy normal fasting subjects secretin was given intravenously at a dosage level of 1 clinical unit per kilogram body weight. One hour later 16 of these subjects received intravenously a second dose of secretin combined with insulin (0.1 unit per kilogram body weight). The remaining 10 subjects at the end of the first hour received a second injection of secretin alone.

The average hourly volumes of duodenal contents recovered were practically identical in both groups of patients. Both groups showed an initial rise in trypsin concentration following secretin injection. In the subjects receiving secretin alone the enzyme concentration then decreased progressively to levels below basal values. In contrast, in the subjects receiving insulin there was a definite increase in enzyme concentration following the insulin administration. In another series of 4 patients with pancreatic disease, the volumes of fluid secreted were within normal limits but all samples, even after insulin administration, showed almost complete absence of enzymes. This dissociation suggests the possibility that normally dif-

ferent secretory units participate in the production of fluid and enzyme.

Presence of a specific gastric hormone (gastrin) in the dog's pyloric mucosa. M. H. F. FRIEDMAN and ELIZABETH N. KING (by invitation). *Dept. of Physiology, Jefferson Medical College, Philadelphia, Pennsylvania*. An extraction procedure used in the preparation of secretin from hog intestine (Friedman and Thomas), differing from those of either Ivy or Komarov, was applied to the mucosa of the stomach and duodenum of the dog in an attempt to isolate "gastrin." Assays of the potency of different extracts to stimulate gastric secretion were made on fasting cats under nembutal anesthesia.

Intravenous administration of 60 mg of pyloric mucosal extracts stimulated gastric secretion. From a control hourly rate of 0.2 cc of alkaline mucus, secretion was augmented to 8 or 10 cc per hour of clear juice with a total acidity ranging from 130 to 140 m. eq. per l. These pyloric extracts had no effect on either pancreatic or hepatic secretion in acute experiments on dogs although duodenal extracts, similarly prepared, had very pronounced secretin-like action on the pancreas and liver.

When determined by the cat blood pressure method pyloric extracts in doses which were effective in stimulating gastric secretion were found to be practically histamine free (less than 0.4 gamma histamine per 60 mg dose). The evidence favors the view that a specific gastric hormone, or "gastrin," exists in the dog's pyloric mucosa. The excitatory effect of the pyloric extract on the gastric glands probably was not due to traces of histamine since (1) the histamine content was less than 6 per cent of the reported threshold dose, and (2) in small doses histamine by intravenous route excites gastric secretion only when given continuously, whereas the pyloric extracts were given in a single dose.

Treatment of non-specific ulcerations of the intestinal tract with extracts of intestinal mucosa. M. H. F. FRIEDMAN, B. F. HASKELL (by invitation), and Wm. J. SWARE (by invitation). *Dept. of Physiology, Jefferson Medical College, Philadelphia*. The hypothesis was entertained that both peptic ulcer and non-specific ulcerative colitis are due to the absence of a factor normally present in the intestinal mucosa. Differences in the lesions are assumed to be due to structural differences in the mucosa of the regions involved. Extracts of hog's small intestine mucosa were fed to seven patients with proved idiopathic ulcerative colitis that were refractory to other forms of treatment. Sigmoidoscopic examination was performed on each patient before and at intervals after commencement of therapy. Results were evaluated by changes in the appearance of the mucosa, frequency

of bowel movements, consistency of stools, presence of blood and mucus in stools, and the overall symptomatic picture. No other medication or special diets were given.

Definite sustained improvement has been shown by six patients while one patient has shown questionable benefit. The first sign of improvement usually was a reduction in frequency of bowel movements, followed by a return of the stool consistency towards normal, and finally disappearance of blood and mucus. The rectosigmoid mucosa showed decrease in friability, disappearance of ulcers, and decrease in hyperemia. Improvement was first noted after 2 to 5 weeks, occurring earlier in patients with illness of less than one year's duration. In an additional case of regional ileitis not benefited by surgery the bowel movements were reduced after 12 days' treatment from 8 loose bloody stools to 2 formed blood-free stools per day.

Final evaluation of the treatment must await study of a larger series of patients and a longer period of observation.

Changes in the distribution of sodium, potassium and water in muscle following release of tourniquets. F. A. FUHRMAN and J. M. CRISMON, *Dept. of Physiology, Stanford Univ. School of Medicine*. Water, sodium and potassium were determined in the muscles of the hind legs of rabbits after removal of tourniquets which had been left in place on one leg for 1, 2, 3 and 4 hours. Samples of muscle from both legs were taken 2 hours after release of the tourniquets. The values given in the table are expressed as excess sodium or water per 100 grams fat-free solids in the muscles of the occluded leg compared to the concentration of these substances in muscles of the opposite leg.

Hours occluded	Gastrocnemius		Tibialis anterior	
	Excess Na (m.Eq.)	Excess H <sub>2</sub> O (gms.)	Excess Na (m.Eq.)	Excess H <sub>2</sub> O (gms.)
1	9.13	65.7	3.85	48.5
2	12.01	86.1	5.67	44.1
3	30.7	193.9	10.72	90.3
4	41.4	201.5	15.37	92.7

After 4 hour occlusion the gain of sodium exceeds the gain of water in the gastrocnemius to such an extent that it is concluded that sodium has penetrated into the intracellular compartment. Such penetration of sodium does not occur after 1 and 2 hour occlusion.

Ablation of area 13 in primates. J. F. FULTON, R. B. LIVINGSTON (by invitation) and G. D. DAVIS (by invitation), *Laby. of Physiology, Yale Univ. School of Medicine, New Haven, Conn.* The posterior portion of the orbital gyrus (Walker, *J. comp. Neurol.* 73:59, 1940) has been ablated in a number of primates. Surgical exposure is readily obtained by

reflecting a large hexagonal calvarium flap hinged on one temporal muscle followed by elevation of the frontal lobes. After unilateral ablations of area 13 no behavioral alterations could be detected and temperature regulation remained normal. Confirming Ruch and Shenkin (*J. Neurophysiol.* 6:349, 1943), bilateral ablation of area 13 consistently resulted in motor hyperactivity quantitatively four to eight times greater than preoperative activity as gauged by a capacitance-regulated activity cage. In adult female monkeys (*M. mulatta*) the hyperactivity is cyclic, with well-defined periods of diminished activity occurring every 28 days and corresponding with the periods of oestrus.

Simple cortical incisions, 4-5 mm deep, around all margins of area 13 fail to induce these activity or temperature-regulatory changes, suggesting that fibers from area 13 ascend vertically into the anterior extremity of the caudate nucleus. [Aided by a grant from The Fluid Research Fund, Yale Univ. School of Medicine.]

Hepato-renal factors in circulatory homeostasis. X. An hepatic enzyme system which inactivates an hepatic vaso-depressor. R. F. FURCHGOTT (by invitation) and EPHRAIM SHORR, *Dept. of Medicine, Cornell Univ. Medical College and The New York Hospital, New York City*. Normal liver slices aerobically inactivate a vaso-depressor principle (VDM) present in plasma and liver in irreversible shock and formed by normal liver on anaerobic incubation. Liver slices from animals in irreversible shock or after a 2 hour anaerobic incubation lose this property. Neither normal nor shocked liver inactivate VDM anaerobically (Shorr, Zweifel and Furchgott, *Science*, 102:489, 1945).

A cell-free saline-phosphate extract of normal liver (rabbit, dog, beef) has been prepared which inactivates VDM aerobically but not anaerobically. Extracts similarly prepared from livers removed during irreversible shock or previously subjected to anaerobic incubation for 2 hours failed to inactivate VDM. It would therefore appear that the VDM inactivation system in normal liver extracts is the same as that in normal liver slices. Since it is only active aerobically, it is tentatively called VDM oxidase.

VDM oxidase has two components: a heat-labile apoenzyme and a heat-stable coenzyme. The coenzyme is precipitable by barium and alcohol, and by mercuric nitrate. Although not yet purified from liver extracts, its fractionation characteristics resemble those of muscle adenylic acid. Muscle, but not yeast, adenylic acid has been found to reactivate the apoenzyme of VDM oxidase.

The coenzyme of VDM oxidase restores the VDM inactivating capacity to both liver slices which have lost this property through previous anaerobic incubation, and to saline phosphate extracts prepared from such slices. [Aided by grants

from the Josiah Macy, Jr. Foundation and the Eli Lilly Co.]

Preliminary observations on dogs subjected to negative "G" by J. L. GAMMA and ROBERT S. SHAW (introduced by H. M. Sweeney) *Aero Medical Lab., Air Materiel Command Wright Field, Dayton, Ohio*. To gain knowledge of pathology resulting from negative  $g$ , anesthetized dogs, harnessed on the human centrifuge in the 'head out' position, were given consecutive two minute runs at 7  $g$  (negative). At this exposure, constant findings were hemorrhages into the mucous membrane of the accessory sinuses, middle ear chamber, and the nasopharynx. Edema and hemorrhage also were noted in the tongue, conjunctivae, and subcutaneous tissue of the sculp. Inconstant findings were atelectasis of one or more lobes of the lung and less frequently large hematomas into the subdura. Some of the animals died during or immediately after the run with respiratory failure preceding cessation of heart beat. These deaths were not necessarily associated with any gross evidence of cerebral hemorrhage. Of the surviving animals, most behaved normally after recovery from anesthesia.

In another group of dogs the first noted evidence of injury during exposure to increasing time  $g$  values was the formation of petechiae in the mucous membrane of the accessory sinuses. A study was then made in which the anterior wall of the frontal sinus was removed and the time of appearance of petechiae in the mucosa during centrifugation to various amounts of negative  $g$  was recorded with a repeating camera. Based on this technique, a time  $g$  curve has been prepared which illustrates increase in tolerance with decrease in time.

Fecal excretion of androgens by the dairy cow during pregnancy. F. N. GASSNER and BLANKARD B. LONGWORTH (introduced by C. A. Minske) *Colorado Agricultural Experiment Station, Fort Collins, and Dept. of Biochemistry, Univ. of Colorado School of Medicine, Denver*. During studies of experimental sex reversal and hormone metabolism in dairy cattle one of us discovered in 1942, independently, that feces from pregnant dairy cows contained large amounts of androgenic substances. Since then the following observations have been made.

Greatest concentration of androgens in feces occurred during the last month of pregnancy. Steer and bull manure were relatively inactive.

These heat labile substances were active by mouth when assayed with cockerels 10 days old. Comb hypertrophy up to 1200 per cent occurred with simultaneous testicular atrophy. Primitive sex cords, characteristic of the embryonal gonad, appeared.

Methyl testosterone and androstenedione were active orally in chicks. The effects of the latter simulated more closely the action of feces than did

the effects of the former. Progesterone was inactive. One kilogram of dried feces contained androgenic potency equivalent to 300 mg of methyl testosterone or 180 mg of androstenedione. Active extracts showed similar potency orally and by combination.

Accessory sex organs of the estrate rat failed to respond to manure feeding, but injections of neutral ketones stimulated their growth.

Characteristic variations in potency occurred from month to month during gestation. Maximum potency was noted during the last week of pregnancy and excretion dropped sharply to zero at calving. The curves of these values resemble to a considerable extent those obtained by Venning (*Ludoeriology* 39: 203, 1946) for urinary corticoid excretion during human pregnancy.

Fecal androgen excretion also occurs during the normal estrous cycle with a peak coincident with corpus luteum maturation.

The effect on rats of large doses of an estrogen, the methyl ether of bis-dehydroisoynolic acid. ROBERT GALT and MILDRED LILLY (by invitation), *Depts. of Biology and Zoology, New York and Syracuse Univ.* Female rats approximating 115 grams in weight received by stomach tube daily either 0.5 or 0.1 mg of the methyl ether of bis-dehydroisoynolic acid (MDDA) for 30 days, or similar doses of ethinyl estradiol (EE). Controls were untreated. Each group approximated 10 animals.

Body weight increases were almost completely suppressed by both doses of MDDA, and reduced to 25% of normal by both doses of EE.

Pituitary weight increased by 156% in animals receiving 0.5 mg doses of MDDA, and by 100% in those receiving 0.1 mg doses. EE produced lesser effects. Adrenal weight increased variably but averaged a 70% rise in the animals receiving 0.5 mg MDDA and 50% in those receiving 0.1 mg. The higher doses of EE produced a 28% increase, the lower doses none. Ovarian weight was reduced variably by all treatments but more by EE than by MDDA. Uterine weights were increased by both doses of MDDA (57% and 45%), but not significantly by EE. Thymus weight was decreased by 46% with both doses of MDDA and by 32% and 18% with the two doses of EE.

Hemoglobin levels did not differ significantly in treated animals from those in untreated controls. Differential counts showed a decrease in lymphocytes of 6 to 10% in all treated groups, with a rise of similar magnitude in neutrophils.

The effects of MDDA, including unreported histological observations, were in general the classic ones of estrogen overdosage. MDDA exhibited in most instances distinctly greater effects than EE. [Aided by a grant from the Ciba Pharmaceutical Products, Inc.]

**Cause of death from explosive decompression at high altitudes** S GELFAN, L F NIMS and R B LIVINGSTON (by invitation) *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn* Unanesthetized rats were suddenly decompressed in a pressure chamber from a simulated altitude of 20,000 feet to altitudes ranging up to 75,000 feet. Continuous recording of respiration and E K G was maintained throughout the experiment. The half-time of decompression was about 0.2 second. The average duration of respiration, with decompressions above 52,000 feet, was 17.8 seconds. Respiration lasted progressively longer below 52,000 feet. It is suggestive that rats would survive sudden decompressions at altitudes below 35,000 feet.

When breathing air, the survival time is independent of the final altitude after decompression as long as the latter is above 52,000 feet. At this altitude the alveolar vapor pressure and probable CO<sub>2</sub> pressure are together about equal to the barometric pressure. The animals therefore die from anoxic anoxia which is as complete at about 52,000 feet as it is at 75,000 feet or higher. Respiration in unanesthetized rats suddenly exposed to pure nitrogen gas stops in 20.7 seconds. The slightly longer survival time is probably due to the residual air in the lungs of the N<sub>2</sub> animals as compared to the sudden complete deflation of lungs during sudden decompression.

While the hearts continue to beat for some minutes after decompression, a sudden marked reduction in rate occurs at about the same time as respiration ceases in both anesthetized and unanesthetized rats. The experiments so far suggest that for survival, the interval between decompression and recompression is a function of the duration of respiration after decompression at any given altitude. [Investigation carried out under Contract W-33-038-ac-14507 (Wright Field) between the Army Air Forces, Air Materiel Command, and Yale Univ.]

**Patterns of muscular innervation in man** ERNST GELLHORN *Laby of Neurophysiology, Univ of Minnesota* Electromyograms are recorded by means of surface electrodes from the flexor and extensor carpi radialis and biceps and triceps during flexion and extension of the wrist in pronation and supination.

It is found that three stages, depending on the degree of stress, may be distinguished. In the first, the activity is confined to the agonist. In the second, action potentials appear in the agonist and a muscle of the upper arm according to the following rule: Biceps activity is associated with flexion of the wrist in supination and its extension in pronation; triceps innervation occurs when the wrist is flexed in pronation or extended in supination. The upper muscles thus selectively called into action are to be synergic with the agonists and co-

determined by the performed movement. In the third stage, under conditions of considerable stress, action potentials appear also in those muscles which are the antagonists of agonist and synergist, but their innervation is so much less than that of the latter group that the characteristic innervation pattern is maintained.

The adaptive character of this innervation pattern is apparent. The co-innervation leads to a slight fixation of wrist and elbow and gives thereby increased stability to the arm. The movement of the latter is accounted for by the difference in the degree of innervation between the principally functioning muscles (agonists and associated synergists) and their respective antagonists.

The practical importance of these observations is illustrated by the fact that in some cases of poliomyelitis a distinct E M G could be evoked in the biceps when this muscle was a synergist in a wrist movement although activity was absent when the biceps was an agonist. A similar statement holds for the triceps. [Aided by a grant from the National Foundation for Infantile Paralysis.]

**The effect of atabrine on the dog heart** MENARD M GERTLER and DOROTHY KARP (introduced by H E Hoff) *From the Dept of Physiology, McGill Univ, Montreal* Shortly after the demonstration by Babkin and Ritchie (Rev Can de Biol 4: 346-368, 1945) that quinine partially paralysed the vagal inhibitory fibres to the dog heart, it was observed by the present authors that atabrine produced the same effect. The action of atabrine further resembles the action of quinine in that both are antagonized by eserine, and both are antagonistic to meclocholyl. This parallelism, and the established efficacy of quinine, an isomer of quinine, in restoring regular sinus rhythm to hearts in auricular fibrillation and paroxysmal (nodal) tachycardia, suggested that atabrine would be similarly effective. Experiments on dogs have confirmed this suggestion. Atabrine, injected intravenously, restored almost immediately regular sinus rhythm in animals with experimentally produced auricular fibrillation and supraventricular (nodal) tachycardia of the vagal type. Atabrine has recently been employed successfully in clinical cases with the same disorders of rhythm.

**Studies of carbohydrate metabolism in South African Negro pellagrins** I Oral and intravenous glucose tolerance tests. THEODORE GILLMAN, JOSEPH GILLMAN and JOEL MANDELSTAM (introduced by C I Reed) *(Anatomy Dept, Univ of the Witwatersrand, Johannesburg, South Africa)* In adult Africans manifesting classical clinical signs of pellagra, carbohydrate metabolism was examined by assessing responses to glucose administered orally and intravenously. Fifty oral and 40 intravenous tolerance tests were performed in more than 30 cases before, during and after different



forms of therapy. Hagedorn-Jensen blood sugar method was used throughout.

Resting sugar was above 120 mgm per cent in 4 cases, being 220 mgm in one. In 4 others fasting sugar was below 65 mgm. In 20 cases the peak level was attained only after 60 to 90 minutes. On previously established criteria for normals (Gillman and Golberg, 1913), glucose storage was delayed in 16 pellagrins blood sugar remaining 15 to 30 mgm above resting level, even after 3 hours. Glycosuria observed in 6 cases. In 1 case the blood sugar curve was flat, the maximal glucose level being 90 mgm. Rate of removal of intravenously injected glucose was calculated by velocity constant. In 22 of 29 pellagrins removal of injected glucose was delayed. In 13 of 20 patients oral tolerance, and in 1 of 6 patients intravenous tolerance remained abnormal after clinical cure was pronounced. Significance of findings discussed in relation to (1) severe initial liver damage, (2) response of liver to therapy as revealed by serial aspiration liver biopsies, (3) lesions of endocrines and other organs. The view is suggested that alterations in carbohydrate metabolism as assessed by above tests depends on (1) previous diet, (2) nature and mode of production of lesions in liver and other organs, and (3) state of organism at time lesions are induced.

Studies of carbohydrate metabolism in South African Negro pellagrins. II. Insulin-adrenalin tolerance tests. THOMAS GILLMAN, JOSEPH GILLMAN and JORI MANDLSTAM (introduced by C. I. Reed) (*Anatomy Dept., Univ. of the Witwatersrand, Johannesburg, South Africa*). In addition to glucose tolerance tests, insulin-adrenalin tests were performed in 32 pellagrins. According to the criteria of Fraser et alia (1941) the response to insulin was normal in 4 cases, insulin sensitivity with severe symptoms or coma was noted in 9 while insulin resistance was demonstrated in 20 cases. Hypoglycaemia responsiveness was observed in 9 patients and hypoglycaemia unresponsiveness in 19. Adrenalin was valueless in relieving hypoglycaemia in pellagrins, as shown by the fact that in 13 patients, 1 cc of 1/1,000 adrenalin administered intramuscularly failed in 11 of 13 instances to raise the blood sugar 20 mgm in one hour. Moreover, in 4 patients who became comatose the blood sugar level, half an hour after adrenalin, remained below 40 mgm per cent and it was necessary in all comatose patients to resort to oral plus intravenous glucose to combat coma. Only a very few patients attained a normal response to insulin, and all of the 19 cases initially hypoglycaemic unresponsive remained so, even when they were pronounced clinically cured. Four patients suffering from severe mental disturbances became perfectly oriented and apparently sane immediately they were revived from the hypoglycaemic coma which supervened during the insulin tolerance tests. The

significance of these findings, in relation to the widespread bodily lesions in the liver, endocrines, nervous system and other organs, was considered.

Junctional delay in the heart of the turtle. A. S. GROSS, JR. *Dept. of Physiology, Washington Univ. School of Medicine, St. Louis*. Data from experiments on turtle hearts in standstill usually plot curves showing short A-V delays after long intervals between stimuli (St-St intervals) and long A-V delays after short St-St intervals. Unlike those from somewhat deteriorated preparations, results of experiments with fresh preparations plot curves with normal A-V times at shorter St-St intervals, less scatter of results and a sharper break at short St-St intervals to long A-V times or failure of transmission. Electrograms may show changes which indicate that major changes of A-V time are associated with slight changes of activation paths.

The results confirm the earlier conclusion that the A-V pause is due to true junctional delays. Any path which first results in ventricular excitation leaves other paths redundant. If the most direct paths, giving minimal A-V time, be the more susceptible to fatigue or be statistically more rare, then failure to excite across such a path leaves the possibility of ventricular excitation by other less direct, multiple junction paths. A wide range of A-V times is thus made possible by complications of junctional delays. Such delays occur close to the anatomical A-V junction and are not to be considered as due to slowed conduction in the usually accepted sense of the term.

Although abnormally short A-V times have not been recorded in this series of experiments, there have been found a few V-A times too short to be accounted for as due to atrial stimulation by electrotonic currents arising during the period of ventricular repolarization.

Stability of thrombin in the presence of fibrinolysin. ANTHONY J. GLAZKO. *Dept. of Biochemistry, Emory Univ., Ga.* The clotting activity of thrombin solutions was found to be unaffected by incubation with blood protease preparations for 2 days at 38°C. Globulin fraction III-3 from human blood, and purified fibrinolysin ("plasmin") were used as the source of protease. These results contrast sharply with the marked thrombolytic action of trypsin, and furnish additional evidence that the blood protease is not identical with trypsin.

Investigation of globulin fraction III-3 showed that thrombin and fibrinolysin were both present. The addition of crystalline soy trypsin-inhibitor to solutions of III-3 interfered with the proteolytic action of fibrinolysin, but did not inhibit the activity of thrombin. The close association of thrombin with fibrinolysin in globulin fraction III-3, and of prothrombin with pro-fibrinolysin in fraction III-2, may be indicative of the potential



importance of fibrinolysin in the blood clotting system

**The effect of pentobarbital anesthesia on the production of irreversible hemorrhagic shock** H GOLDBERG (by invitation), FRANK ROEMHILD (by invitation), HAROLD C WIGGERS and RAYMOND C INGRAHAM *College of Medicine, Univ of Illinois, Chicago, Illinois* Anesthesia has been reported both to delay and to hasten the development of the *irreversible shock state* in animals subjected to hemorrhagic hypotension

In this laboratory, untreated control dogs, subjected to a 90 minute period of hemorrhagic-hypotension at 40-43 mm of Hg, pass from an *impending* to an *irreversible shock state* in 58.3 per cent of the animals studied

In the present series of 13 dogs, a surgical level of anesthesia was established by the intravenous injection of sodium pentobarbital (14-28 mgm / kgm) prior to the institution of hemorrhagic-hypotension procedures. The mortality rate among these animals was approximately identical (53.8 per cent) to that in the series of 12 control animals (58.3 per cent). The median post-reinfusion survival time in those animals receiving anesthesia was, however, markedly lengthened (20 hours as compared with 12 hours in the control series)

These findings indicate that the use of sodium pentobarbital to produce surgical anesthesia does not, when properly administered, accelerate the transition from *impending* to *irreversible shock*. On the contrary, it may in these doses prove of some minor benefit

**The dependence of carbon monoxide uptake of the body on respiratory minute volume** DAVID E GOLDMAN (introduced by B G King) *Naval Medical Research Inst, National Naval Medical Center, Bethesda, Maryland* Semi-empirical equations for the rate of carbon monoxide uptake by man have been given by Forbes, Sargent and Roughton, and by Pace, Consolazio, White and Behnke. The rate of uptake is linear with time up to about one-third of the equilibrium value of COHb in blood. For this range one can construct an expression for the rate of uptake based on simple physical considerations as to breathing and alveolar gas exchange

Under normal conditions, where the tidal volume is not too large with respect to the average volume of gas in the alveoli and where the breathing pattern does not deviate too much from a zigzag line, the following basic relation is derived

$$R = \frac{DM}{D + M} C_0$$

here  $R$  is the rate of carbon monoxide absorption by the body,  $D$  is the diffusion constant of carbon monoxide for the alveolar membrane,  $M$  is the

alveolar minute volume, and  $C_0$  is the carbon monoxide concentration in the ambient air

This relation agrees fairly well with the experimental data of Pace, et al, and has the advantage of indicating relevant parameters. It also offers an explanation of the fact that somewhat less than half of the carbon monoxide inhaled is absorbed into the blood

Analysis of the basic differential equations and their solution permits an estimate of the errors made by the approximations. [The opinions or conclusions contained in this report are those of the author and are not to be taken as necessarily reflecting the views of the Navy Department.]

**The relation between plasma protein concentration and T-1824 disappearance rate in plasma volume determination** FRANK GOLLAN (introduced by M B Visscher) *Dept of Physiology, Univ of Minnesota Medical School, Minneapolis* Plasma volume determinations in 30 infants suffering from severe malnutrition have shown great variation in disappearance rates of the dye T-1824 injected into the bloodstream. Instead of the average disappearance rate of T-1824 of 8.8 per cent per hour found in normal adults the disappearance rate in these children varied from 4 to 34 per cent with an average of 16 per cent. Because of the great variation in the disappearance rate in infants it is imperative to take at least two blood samples in order to extrapolate the dilutions of the dye to zero time

Plasma protein values ranged from 4.8 to 8.8 grams per cent and albumin from 3.0-4.5 grams per cent. In correlating the disappearance rate of the dye with the plasma protein level it could be shown that there exists an inverse correlation with a reliability factor of 3.7 (Statistically significant if higher than 2)

This inverse correlation between plasma protein level and the disappearance rate of T-1824 stresses the necessity of extrapolating the disappearance of the dye from the blood stream to zero time whenever changes in the plasma protein level are expected

**The effect of adrenalectomy on the oxygen consumption of testis of testosterone-treated normal rats** JORGE GONZALEZ Q (by invitation) and CLIFFORD A ANGERER *Dept of Physiology, The Ohio State Univ, Columbus* Young white rats (20-30 grams) were divided into 6 experimental groups: (1) normal rats, (2) adrenalectomized rats, two groups of normal rats which received intraperitoneal injections of (3) 1 mg (light dosage), or (4) 5 mg (heavy dosage) testosterone propionate (Perandren-Ciba)/kg/rat/3 times/week/6 week period, and two groups (5, 6) treated as in "3" and "4" but adrenalectomized at least 4 days prior to experimental use. Respiration of the testis was studied by the Warburg manometric technique

The tissue was prepared as follows: the right testicles from ca 6 rats, weighing from 80-120 grams and starved from 18-21 hours prior to use, were deprived of their tunica, were minced, and were pooled. To 200 mg samples (by torsion balance) was added 0.5 cc Krebs  $\text{PO}_4$  Ringers solution. To each of 6 respiration flasks was added 0.5 cc of this Krebs testicular mixture to 2.0 cc Krebs' solution. This solution had been buffered previously to pH 7.4 with  $\text{NaHPO}_4$ . 1 gnl portions of the mixture were placed in individual vials and dried overnight at  $105^\circ\text{C}$  in order to obtain the dry weights of samples of testicular tissues. The experiments were performed in an atmosphere of pure oxygen and at a temperature of  $37.5^\circ\text{C}$ . The results are expressed as  $\text{QO}_2 = -\text{mm}^3\text{O consumed/mg (dry wt) testis/hr}$ . The numerals appearing in parentheses denote the number of rats used and also the number of experiments performed: normal rats  $-1.8 \pm 0.18$  (16), adrenalectomized rats,  $-3.1 \pm 0.21$  (25), normal rats treated with light dosage of testosterone,  $-1.3 \pm 0.26$  (18), and with heavy dosage,  $-2.7 \pm 0.11$  (15), adrenalectomized rats previously treated with light dosage  $-2.1 \pm 0.16$  (20), and with heavy dosage,  $-2.2 \pm 0.12$  (19) of testosterone.

The effect of various substrates on the oxygen uptake of thymus in adrenalectomized rats. JAMES GONZALEZ Q (by invitation) and CLIFFORD A. ANGELER Dept of Physiology, The Ohio State Univ., Columbus. The rats used in these experiments may be divided into 2 experimental groups: adrenalectomized and unoperated (control). The operated animals were not used until after the fourth day following adrenalectomy. Thymus were removed from 6-10 male white rats which weighed from 80-120 grams and were starved from 18-21 hrs before the experiment. Thymus were minced and ca 100 mg samples were placed in respiration flasks which contained 2.5 cc Krebs Ringer solution. This solution was buffered at pH 7.4. The respiration was studied by the Warburg technique, in an atmosphere of pure oxygen, and at a temperature of  $37.5^\circ\text{C}$ . The oxygen uptake was expressed as  $\text{QO}_2 = -\text{mm}^3\text{O consumed/mg (dry wt) /hr}$ . The respective substrates were dumped from the side arms of the respiration flasks at the close of an initial hour's run (control). The results are as follows: unoperated rats  $-\text{QO}_2 = -3.07$  (41 expts) with the oxygen uptake being increased, by glucose +25%, and by pyruvate +22%, adrenalectomized rats  $-\text{QO}_2 = -3.32$  (62 expts) with the  $\text{QO}_2$  being decreased by glucose -3%, by lactate -10%, and by succinate -4%.

Weight changes in various endocrine glands of normal rats after prolonged treatment with testosterone. JAMES GONZALEZ Q (by invitation) and CLIFFORD A. ANGELER Dept of Physiology, The Ohio State Univ., Columbus. Young, male, white

rats (20-30 grams) were divided into 3 experimental groups: 1) controls, and two groups which received intraperitoneal injections of 2) 1mg (light dosage) or of 3) 5 mg (heavy dosage) testosterone propionate (Permdren Ciba)/kg /rat/3X/week/6 week period. The rats were reared under regular laboratory conditions at  $78^\circ\text{F}$  (controlled). They were weighed periodically. After 6 weeks, when the individual rats' weight was between 80 and 120 grams, they were weighed, sacrificed, measured from snout to anus, and the following organs rapidly, but carefully, dissected: adrenal, hypophysis, testis, thymus and thyroid parathyroid. The weighed glands were placed in individual vials and dried overnight at  $105^\circ\text{C}$ . The data, on statistical treatment, showed the following significant decrease in organ weights for testosterone treated, normal rats as compared with their controls: a) Wet weights, 1) light dosage—adrenal, hypophysis, testis, 2) heavy dosage—hypophysis, testis, thymus, b) Dry weights, 1) light dosage—adrenal, 2) heavy dosage—hypophysis, testis, thymus. The results suggest the following conclusions: 1) Low dosage produces a negative water shift in at least the hypophysis and testis. 2) Higher dosage shows a decrease in the solid matter of the hypophysis, testis, thymus. 3) Paradoxically, light doses decrease, while heavy doses have no effect on, the wet and dry adrenal weights. 4) Prolonged testosterone treatment in the concentrations studied has no effect on body length and body weight.

Axon surface structure and interactions. HAROLD T. GORDON (introduced by John H. Welsh). Biological Labs., Harvard Univ. Many non-polar organic molecules, whose size and shape lie within definite steric limits, adsorb on the surface of the nerve axon (in Crustacea). This non specific interaction lowers the stability of the axon. The degree of interaction is measured indirectly, by counting the number of nerve impulses in the repetitive discharge set up by a single impulse, or by determining the concentration of calcium ions necessary to counteract the unstabilizing effect. Quantitative studies of the molecular and ionic interactions suggest a working hypothesis concerning the nature of the axon surface.

Polar groups (possibly phosphoryl, amino, hydroxyl, or carboxyl groups of lipids or proteins) occur in the axon surface at intervals of about  $3 \text{ \AA}$ . A fraction of the available pairs are weakly bridged by calcium ions. These stabilizing cross links are probably broken during the passage of a nerve impulse, and "recalcification" is one factor in the recovery process (phase of negative after potential). Non polar areas of diameter near  $8 \text{ \AA}$  are in close association with the polar areas. Molecules adsorbed on the non polar areas cause a shift in the calcium equilibrium, possibly by altering the spatial position of the polar groups.

It is possible that analogous surface interactions and induced secondary changes may explain the physiological activity of carcinogens, of "organizers," and of steroid hormones

**Adrenaline induced auricular fibrillation in the dog** RONALD GRANT, M M GERTLER and K GODWIN TERROUX (introduced by H E Hoff) *From the Dept of Physiology, McGill Univ, Montreal* Auricular fibrillation is a usual accompaniment of hypothermia in man. In an attempt to reproduce the fibrillation of hypothermia in dogs, twenty-eight dogs were cooled by ice-packing, under either Nembutal or Pentothal sodium anaesthesia, discontinued at the onset of cold narcosis. In no case did fibrillation occur spontaneously with cooling. Auricular fibrillation was induced experimentally in both cooled dogs and dogs at normal body temperature by stimulation of the vagi in five out of a series of nine dogs. In a second series of six animals fibrillation was induced in four by intravenous injections of adrenaline. This adrenaline induced fibrillation occurred only with functional vagi. In dogs in which the vagi were blocked by local cooling, the adrenaline effect was reversibly inhibited. The most reliable method of inducing auricular fibrillation was by intravenous adrenaline injection followed by vagal stimulation, which was effective in five out of a series of seven dogs, in none of which did vagus stimulation alone produce fibrillation. In one dog, decerebrated four hours previously under ether, adrenaline followed by vagus stimulation induced fibrillation. The results re-emphasise the importance of increased vagal tone in auricular fibrillation, and are in general consonant with the hypothesis of Nahum and Hoff, that fibrillation depends on the interaction of two factors, an increased vagotonia and the presence of some agent which increases the inherent excitability of heart muscle.

**The relation of O<sub>2</sub> tension in bone marrow blood to the erythropoiesis following hemorrhage** WILSON C GRANT (by invitation) and WALTER S ROOT *College of Physicians and Surgeons, Columbia Univ, New York City* The general belief that the stimulus for erythropoiesis is low O<sub>2</sub> tension in bone marrow has been based on indirect measurements. We have obtained direct evidence on 10 unanesthetized dogs by inserting a needle 2.5 cm into the head of the humerus. The animals are not excited and blood soon fills the needle. O<sub>2</sub> content, O<sub>2</sub> capacity, and hematocrit values were obtained on the first 0.15 cc. The above measurements were carried out on jugular venous blood and in addition erythrocyte and reticulocyte counts were made. pO<sub>2</sub> was calculated from the O<sub>2</sub> dissociation curve of dog blood.

After a 30 per cent hemorrhage, analyses were performed regularly for 3 weeks. Typically, in marrow blood, O<sub>2</sub> decreased from control value of

17.8 vols per cent, 89 per cent saturated, pO<sub>2</sub> 60 mm Hg to 4.2 vols per cent, 24 per cent saturated, 20 mm Hg 25 minutes after bleeding and next day was 13 vols per cent, 87 per cent saturated, 59 mm Hg. Later, O<sub>2</sub> content, O<sub>2</sub> capacity, and hematocrit values in marrow and venous blood rose towards control levels, marrow blood recovered more rapidly.

Direct pO<sub>2</sub> measurements confirmed those obtained by calculation. 1.4 cc were required for this determination, and probably some blood was removed from marrow venous drainage. Since small, successive samples of marrow blood yield approximately equal O<sub>2</sub> contents, we suggest that the agreement between direct and indirect pO<sub>2</sub> measurements cannot be fortuitous.

Marrow blood pO<sub>2</sub> is depressed after hemorrhage, but control level is reestablished in a few hours. Erythropoiesis occurs in the ensuing weeks, although bone marrow pO<sub>2</sub> is not low.

**Anoxic variations in human performance** D M GREEN (introduced by R Frederick Becker) *School of Medicine, Univ of Washington* Fifty male subjects were exposed to four flights in a low pressure chamber at a simulated altitude of 17,000 feet. Rate of ascent and time at altitude were constant. Age, diet, living and working conditions of the subjects were comparable. The subjects were scored on performance in a battery of five tests at ground level and after 60 to 75 minutes at altitude. The battery included arithmetic, cube placing, pursuit, visual discriminatory and visual field perimetry tests.

Average change in scores of individual subjects on particular tests ranged from plus 15.6 to minus 64.4 per cent of the ground level value. Over-all impairment in individual performance at altitude varied from minus 2 to minus 29 per cent and averaged minus 15.7 per cent.

Average impairment in group performance at altitude on individual tests ranged from minus 7.8 to minus 26.1 per cent. Analysis showed these differences to be significant.

In no single test did the degree of anoxic impairment correlate closely with that demonstrated by the test battery as a whole, the correlation coefficient for the various tests varying from plus 0.18 to plus 0.52. Correlation between individual tests was not significant.

It was concluded that the over-all performance of the individual under anoxic conditions represents a composite result of alterations in many functions, not similarly affected by the same degree of anoxia. Hence the selective value of single tests in singling out individuals either susceptible or resistant to anoxia is apt to be low.

**Vasodilator substance present in urine** HAROLD D GREEN, J MAXWELL LITTLE, JOSEPH HESTER (by invitation) and HELEN HILDERMAN (by invitation)

tation) Dept of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College Winston Salem, N. C. In studies of ischemic compression shock urine, repeatedly injected intravenously, caused temporary depression of arterial pressure with each injection (Green, Little, and Hawkins, Fed. Proc. 5: 36, 1916)

This report summarizes the cardio dynamic responses seen after each of ten 25 ml. injections of urine into 1 additional dogs

Cardiac output (CO) measured by the O difference method, venous samples being obtained by right ventricular catheterization, increased 10 to 180%,  $\text{av} +78\%$ , mean arterial pressure (MAP) declined 10 to 40%,  $\text{av} -27\%$ , and peripheral resistance (MAP/CO) decreased 1 to 65%,  $\text{av} -42\%$

Aortic pulse pressure, recorded optically, increased, left intraventricular diastolic pressure, recorded by catheterization of left ventricle via left carotid artery, decreased, right intraventricular systolic pressure increased, right intraventricular diastolic pressure and right intra atrial pressure decreased

During the first 30 sec. pulmonary O uptake increased whereas venous O content was unchanged, after 1 min. venous O content was increased whereas pulmonary oxygen uptake had usually returned to normal. Complete recovery of cardiac output, mean arterial pressure, etc. required 0.5 to 1 hour

The injections evidently caused peripheral arteriolar vasodilation and probably also enhanced myocardial contractility. No essential difference was noted between the responses to plain urine, to urine dialyzed until free of  $\text{Cl}^-$ , or to boiled dialyzed urine

In a few preliminary experiments MAP declined and recovered in a similar manner after each of 25 or more injections at 15 min. intervals [Supported by a grant from the Life Insurance Medical Research Fund]

**Alteration of carbohydrate metabolism in hypopituitarism in man** JAMES A. GREENE, *Baylor Univ. College of Medicine*. The carbohydrate metabolism of nine subjects with hypopituitarism was obtained from the gaseous exchange measured in an open circuit metabolism chamber. The subjects were studied in the chamber for a period of 24 hours after an 8 hour period for equilibration. They ingested standard diets of an average composition. The non-protein respiratory quotient varied from 0.671 to 0.772. The dextrose oxidized for the 24 hours calculated by the usual method varied from 19.6 grams formed from fat to approximately 50 per cent of the intake. The non-protein respiratory quotient of two prepubertal boys was 0.858 and 0.862 and each oxidized approximately 100 per cent of the carbohydrate

intake. The data indicates that there is a disturbance in the intermediate steps of carbohydrate metabolism in such instances which are related directly or indirectly with the lack of a hormone or hormones from the anterior pituitary gland. The diminished utilization of carbohydrates in hypopituitarism as shown in our subjects is contrary to the general opinion. Comparable studies in man, however, have not been reported.

The oxidation of dextrose has been increased in two instances following the administration of an extract of the anterior pituitary gland. In one it was restored to normal and improved in the other. Definite subjective and objective response to the administration of methyl testosterone failed in two instances to increase the dextrose oxidation.

**The composition of crystalline secretin picrolonate** HARRY GREENGARD, M. L. WOLFROM (by invitation) and R. K. ARS (by invitation) *From the Dept. of Physiology, Northwestern Univ. Medical School, and the Dept. of Chemistry, The Ohio State Univ.* Secretin picrolonate (*Am. J. Physiol.* 124: 427, 1938) is uniformly crystalline on the basis of microscopy and X-ray diffraction patterns. It is split by warm nitroethane ( $80^\circ\text{C}$ ) into soluble and insoluble portions. The former, which crystallizes out on cooling, is aniline picrolonate in the case of material not subjected to pyridine ether recrystallization, and pyridine picrolonate after applying such a procedure. Identification was effected by decomposing the picrolonates, isolating appropriate derivatives, and establishing by mixed melting point determinations their identity with similar derivatives from known aniline or pyridine. The water soluble residue from the nitroethane treatment manifests on the pancreas the typical secretin action, which is entirely absent from the nitroethane-soluble fraction.

The X-ray diffraction pattern of secretin picrolonate before recrystallization is identical with that of aniline picrolonate, and after recrystallization with that of pyridine picrolonate. Hence the crystalline secretin employed actually exists as mixed crystals, an aniline secretin picrolonate or a pyridine secretin picrolonate complex. The aniline was obviously added in the previous purification and replaced by pyridine during recrystallization. The secretin picrolonate residue from the nitroethane treatment has been uniformly amorphous and yields no X-ray diffraction pattern.

The picrolonic acid content of the various preparations is somewhat variable and considerably lower than stated previously, being 55 to 65 per cent on the unrecrystallized material, 45 per cent after two recrystallizations, 41 per cent after three recrystallizations, and about 30 per cent on the nitroethane insoluble residue. The latter, converted to the hydrochloride, again yields a picrolonate with this same content. The crystal

When a piece of antral mucosa is excised from the stomach of a rabbit and the animal is placed on its usual rough diet, a "chronic ulcer" requiring several months to heal results. In 18 rabbits excision ulcers of the posterior wall of the pyloric antrum averaging 498 mm<sup>2</sup> in area were produced surgically through an anterior gastrotomy under ether anesthesia. When sacrificed 10 days postoperatively the average area of the healing ulcer was 155 mm<sup>2</sup>. In 17 other rabbits which had been treated for 30 days prior to operation with 30 mg of "enterogastrone" concentrate subcutaneously daily, the average area of the ulcer at surgery was 559 mm<sup>2</sup>, and the average area of the healing ulcer on the tenth postoperative day was 49 mm<sup>2</sup>. The difference between the means of the areas at necropsy in the treated and control groups was statistically significant ( $P < 0.01$ ).

**Quantitative measurements of a fibrinolysin inhibitor in the plasma of various species.** M. MASON GUEST, BYRNE M. DALY (by invitation), ARNOLD G. WARE (by invitation) and WALTER H. SIEGERS (by invitation) *Dept. of Physiology, Wayne Univ. College of Medicine, Detroit, Michigan*. A quantitative method has been developed for assaying the fibrinolysin inhibitor activity of plasma. The availability of an active fibrinolysin preparation, derived from bovine plasma (Loomis, *et al.*, *Arch. of Biochem.* 12, 1, 1947) has made this procedure possible.

When a standardized solution of fibrinolysin is mixed with diluted plasma a portion of the fibrinolysin activity disappears. About 1 hour is required for equilibrium and at that time the still active portion of the fibrinolysin is measured quantitatively by its ability to dissolve a standard fibrin clot. The difference between the initial fibrinolysin concentration and the concentration at equilibrium represents the activity of the inhibitor.

The ability of plasma to inactivate fibrinolysin varies, depending upon the species of animal. It is necessary, therefore, to establish the relationship between the degree of inactivation of fibrinolysin and the plasma concentrations in each species for which an assay is desired. Quantitative assay procedures for the inhibitor activity of the plasmas of man, dog, horse, cow, pig, sheep, rabbit, guinea pig, rat, opossum, chicken, turtle and alligator and frog have been established. It has been found that the inhibitor activity of bovine and guinea pig plasma is high, that of the chicken and the cold blooded animals is low, while the plasmas of man, the dog and the rat are intermediate in their ability to inactivate bovine fibrinolysin. [Aided by a grant from the National Institute of Health. Fibrinolysin was supplied by E. C. Loomis of Parke, Davis and Company.]

A simplified technique for the quantitative colorimetric estimation of pregnandiol in urine

H. S. GUTERMAN and M. S. SCHROEDER (introduced by R. Levine) *Dept. of Metabolism and Endocrinology, Research Institute, Michael Reese Hospital, Chicago, Illinois*. The simplified procedure for the qualitative determination of pregnandiol, previously reported from this laboratory, (*J. Clin. Endocrinol.* 4, 262-267, 1944) has been extended to permit quantitative colorimetric measurement of this steroid.

Evidence that pregnandiol is the steroid which is extracted by this procedure is based on spectrophotometric absorption and on melting point data. The addition of other steroids to urine does not interfere with the determination of pregnandiol. The depth of color developed when conc. H<sub>2</sub>SO<sub>4</sub> is added to the pure extracted material is proportional to the concentration of pregnandiol when measured at 420-430 mμ. Recovery of pregnandiol from female urine to which "sodium pregnandiol glucuronide" has been added amounts to 90 per cent of the actual pregnandiol present in the added compound.

The technique, first presented as a diagnostic test for pregnancy in which a visual interpretation of the color was made, is now adapted for use on the colorimeter. The minimal amount of pregnandiol indicating early normal pregnancy is 0.4 mg per 100 cc of the first morning urine specimen. Data relative to the quantitative excretion of pregnandiol in early normal and abnormal pregnancies are reported.

**The effect of sodium dehydrocholate on dog bile.** MARTIN GUTMANN (by invitation), J. WENGER (by invitation), and A. C. IVY<sup>1</sup> *Dept. of Physiology, Northwestern University Medical School*. Dehydrocholic acid in the past has been considered to be a hydrocholeric as defined by Ivy in 1943. However, in 1946, Boyd, Perry, and Stewart presented evidence which appeared to throw doubt on this interpretation.

Studies on twelve acute dogs, anesthetized with pentobarbital, with the cystic duct clamped off, were carried out. Twenty mg per kg of sodium dehydrocholate were administered to flush the system with hepatic bile. After 2½ hours the rate of secretion had returned to normal, and a control sample was collected. Then 20 mg per kg of sodium dehydrocholate was again injected, and bile was collected for one hour. The increase in the rate of flow after dehydrocholate averaged 365%. The concentrations of cholic acid, bilirubin, cholesterol, and total solids decreased 60, 40, 26 and 44% respectively. The hourly output of the above constituents increased 63, 155, 230, and 175% respectively. The specific gravity dropped from 1.0179 to 1.0145. The viscosity dropped from 1.698 to 1.295.

In addition nine unanesthetized chronic bile fistula dogs received 0.5, 1.0, 1.5, 2.0, and 3.0

<sup>1</sup> Now at University of Illinois College of Medicine

grms of sodium dehydrocholate orally per day. The average increase in daily bile output was 21, 35, 24, 69, and 95% respectively. The cholic acid output decreased 21, 7, 22, 14, and 47% respectively. Pigment output decreased 57%, increased 28%, decreased 45, 3, and 2% respectively. The daily output of total solids increased 7, 17, 19, 35, and 43% respectively. The total solids per cc of bile decreased in every instance with one exception (3.0 gm dehydrocholate), the viscosity decreased in every case.

The results show that sodium dehydrocholate is a hydrocholeretic.

**Retinal sensitivity contours in retinitis pigmentosa.** 1. Sensitivity to white light. CHARLES HAIC and SAMUEL L. SALTZMAN (by invitation). *Dept of Physiology and Ophthalmology, New York Medical College.* In dark adapted eyes, the minimal perceptible brightness of a 2 degree test field illuminated for 0.2 second was determined with central, 2, 4, 6, 8, 10 and 20 degree fixation nasally and temporally to the fovea.

In normal eyes, sensitivity (1/threshold) increases from the fovea outward by a factor of about 100. In 25 severe cases of retinitis pigmentosa, sensitivity decreased from the fovea outward, the central area being least affected. In 4 milder cases functional impairment of the central areas was greater than that of certain areas in the periphery.

These findings are contrary to the general belief that the central retinal areas are spared in the early stages of this disease. It is probable that initially the entire retina is functionally involved, but that in later stages the rate of degeneration in the periphery accelerates such that the central areas are relatively spared. It is thus possible that loss of light-sensitivity in the central and para-central areas would prove a useful diagnostic sign of early retinitis pigmentosa.

Filatov has reported arrest of the disease and functional improvement in a high percentage of cases after intramuscular injection of pasteurized cod liver oil. Six of our patients reported subjective improvement after 12 injections of 3 to 2 ml of cod liver oil (prepared by Wyeth, Inc.). In one case we observed a temporary improvement in retinal sensitivity. [Aided by grants from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association, and the American Soviet Medical Society.]

**A method of estimating the total volume of the pancreatic islets in small animals.** R. C. HAIST and E. J. PUGH (by invitation). *Dept of Physiology, Univ of Toronto, Toronto, Canada.* Fresh tissue preparations stained intravitaly with neutral red are used for the estimations. The pancreas is removed and its volume estimated. It is kept cold and made ready for examination by pressing small portions between special glass plates. All the pan-

creas is examined. Each preparation is placed in a microprojector and the total islet area obtained by a planimeter arrangement. The procedure is designed to give (1) a permanent record of the islet outlines, (2) the number of islets, (3) the total area of the islets, (4) the total area of the preparation. Knowing the initial volume of the pancreas and the relation between islet area and total pancreatic area in the pressed tissue, the islet volume can be estimated.

The increase in islet volume with age and the effect of fasting will be shown.

**Experimental treatment of muscular spasticity.** NORMA M. HAJEK (by invitation) and H. M. HINES. *Dept of Physiology, State Univ of Iowa, Iowa City.* A study of the response of spastic muscle to treatment by curare, prostigmine, di-isopropyl fluorophosphate, ammonium chloride or electrical stimulation was made to determine their therapeutic efficacy. The condition of spasticity was produced in the gastrocnemius muscles of albino rats by the injection of a standardized dose of tetanus toxin into the popliteal space of the hind limbs. The various treatments were initiated during the onset of the spasticity.

The therapeutic value was measured by the weight and by direct and indirect stimulation determination of total strength and strength per gram weight of both the experimental and control muscles after a set period of treatment.

The results provided evidence that curare, while it relaxed the muscle for short periods of time, did not prevent atrophy or loss of strength. Prostigmine showed similar negative results. Ammonium chloride injections with the subsequent condition of acidosis, also produced negative findings. Di-isopropyl fluorophosphate injections were seen to hasten the onset and increase the severity of the spasticity. The therapeutic value of this substance therefore, is also negative. Electrical stimulation succeeded in lessening the degree of weight loss while it had no effect on the strength per gram weight. A tendency has been shown by these results that muscle spasticity may best be treated by physical rather than chemical measures.

**The effect of sugar and other food materials on the increased spontaneous activity induced by caffeine.** JOHN HALDI, WINFREY WYNN (by invitation) and CHARLES ENSOR (by invitation). *Laby of Physiology, Emory Univ, Emory Univ, Georgia.* Employing the method described by Schulte and his associates (*Proc Soc, Exp Biol and Med* 42:242, 1943) we have confirmed their finding that caffeine increases the spontaneous activity of the albino rat. Experimental data will be offered to show that this action of caffeine can be neutralized to a large extent by the administration of sucrose.

We have been unable up to the present time to explain the mechanism involved. At first it was

thought that the effect might be due to a specific action of sugar, but it was found upon further experimentation that a similar effect could be obtained when peptone or vegetable oil was administered simultaneously with caffeine. Agar was ineffective showing that the mere presence of other substances besides caffeine and water in the gastrointestinal tract could not account for the neutralizing action of the food materials.

Other experiments ruled out the possible explanation that the effect might have been due to an interference with the absorption of caffeine by the presence of the food materials. The neutralizing effect was obtained (1) when caffeine was injected intraperitoneally and sucrose solution given by stomach tube, (2) when sucrose was administered 30 minutes after caffeine. At this time the caffeine had been absorbed and had produced the characteristic increase in activity.

**Reduction of the amplitude of muscle contraction by application of moist heat to overlying skin.** V. E. HALL, E. MUÑOZ (by invitation), and B. FITCH (by invitation). *Dept of Physiology, Stanford Univ., California.* The gastrocnemius muscles of etherized cats were caused to contract by maximal single break shocks applied to the peripheral end of the last lumbar ventral root at a rate of 56 per minute. Application of hot moist (Kenny) packs to the skin over the muscle during such stimulation often caused a slowly developing reduction in the amplitude of contraction. Anesthetization of the skin with butesine completely abolishes this effect. Application of hot packs when the muscle is activated by stimulation of the peripheral end of the cut sciatic causes no change or a slight increase in contraction. It is concluded that the heat stimulates cutaneous receptors which reflexly decrease contraction amplitude, possibly by evoking vasoconstriction and reduction in blood flow through the muscle.

**The histamine content of gastric juice.** G. A. HALLENBECK, CHARLES F. CODE and R. A. GREGORY (by invitation). *Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.* A preliminary report of this study was made at a previous meeting of the Federation (Federation Proc. 15, March, 1942). Since then additional data have been obtained and the investigation has been completed. The method of histamine extraction has remained the same throughout the investigation (see previous abstract). An alcoholic extraction step was used in order to reduce the potassium content of concentrated extracts because it was found that otherwise the potassium present interfered with the assay of histamine. All gastric juice was obtained from Pavlov, Heidenhain or transplanted types of gastric pouches in dogs. The findings may be summarized as follows:

1 Gastric juice secreted in response to the injection of histamine contained histamine activity as a rule. In some samples, however, none was detectable.

2 Gastric juice secreted in response to mecholyl uniformly contained readily estimable quantities of histamine activity but the amount of activity present bore no relationship to the rate of secretion of hydrochloric acid.

3 Gastric juice secreted in response to insulin hypoglycemia usually contained histamine activity.

4 Three fourths of the samples of gastric juice secreted from Pavlov pouches in response to the feeding of a meat meal contained histamine activity. When present in estimable quantities its concentration in the juice was greater during the first hour after the meal than subsequently.

5 Results of these experiments are consonant with the concept that histamine may be a final common pathway for a variety of physiologic mechanisms which lead to excitation of the gastric secretory cells.

**Variations in visual thresholds during carbon monoxide and hypoxic anoxia.** M. H. HALPERIN (by invitation), J. I. NIVEN (by invitation), R. A. MCFARLAND and F. J. W. ROUGHTON (by invitation). *Dept of Medicine, Boston Univ. School of Medicine, Evans Memorial, Massachusetts Memorial Hospitals, and Division of Research, Harvard Univ. School of Business Administration, Boston, Mass.* The comparative and combined effects of carbon monoxide and hypoxic anoxia on human visual intensity discrimination, as well as the effects of normal and high O<sub>2</sub> atmospheres during recovery from CO, were investigated.

In previous studies we have found that the measurement of visual intensity discrimination thresholds at a low level of illumination provides a very sensitive, useful and precise quantitative index of the physiological disturbance caused by oxygen deprivation. We therefore applied the same technique in measuring the effects of small amounts of CO. Extensive studies were carried out on four well-trained subjects.

A given increase in % COHb in the blood at sea level produces an effect approximately equal to that of an equal decrease in % O<sub>2</sub>Hb due to hypoxic anoxia. At simulated high altitudes, a given % COHb produces an impairment equivalent to a further ascent which would cause an equal additional decrease in % O<sub>2</sub>Hb. The visual threshold is therefore much more sensitive to CO than are other physiological functions so far investigated.

In studying the recovery from CO, we found that the inhalation of oxygen, in addition to its value in accelerating the elimination of CO, had another beneficial effect as compared with the inhalation of ordinary air. An added improvement equivalent to a decrease of about 5 to 7% COHb was produced by breathing oxygen. When the sub-



jects then breathed ordinary air, the thresholds were again impaired by this amount. If, instead of oxygen, the subject breathed ordinary air through out the recovery period, the visual thresholds failed to recover as rapidly as the % COHb declined.

The effect of local compression upon blood flow in the extremities of man. M. H. HALPERIN, C. K. FRIEDLAND and R. W. WILKINS (introduced by H. O. HATHRILLS) *Dept. of Medicine, Boston Univ. School of Medicine, and the Pians Memorial, Massachusetts Memorial Hospitals, Boston, Massachusetts*. The effect of local pressures of 10 to 50 mm Hg on the extremities was investigated by three methods: (a) thermometric, (b) blood gaseometric, and (c) plethysmographic. The results indicated that remarkably low local pressures impair the circulation. Skin temperature measurements show a definite effect with pressures as low as 20 mm Hg. At this pressure, the arteriovenous oxygen difference rises about 25%, and plethysmographic tracings show an equal decline in blood flow. With a local pressure of 30 mm Hg blood flow decreases about 35% both by the A-V oxygen and the plethysmographic methods. Even at 10 mm Hg the plethysmograph revealed a 10% decline in blood flow.

These findings are of importance in relation to the application of constricting dressings or apparatus to the limbs, and to the design of clothing, gloves, and shoes especially for use in extremely cold environments.

Some immediate responses to a sudden reduction in peripheral resistance. W. F. HAMILTON and JOHN W. REMINGTON *Dept. of Physiology, Univ. of Georgia School of Medicine, Augusta, Georgia*. By means of a recently described method the stroke volume, ventricular work and total peripheral resistance were calculated from successive optically recorded pulse pressures.

The abdominal aorta was occluded by means of finger pressure so as to produce a reactive dilation of the peripheral bed below the occlusion. The dilation occurred during the occlusion, and was evident from a change in the diastolic slope before the first beat succeeding release. With this first beat a large increase in stroke volume, a sudden increase in ventricular work, and an immediate decrease in peripheral resistance could be shown. It is suggested that the changes in cardiac work and stroke volume are in response to the change in peripheral resistance. They occur too quickly to be of reflex origin and are probably due to the fact that the mechanical conditions against which the heart is working have been suddenly altered. The contracting heart seems to exert elastic tension and can shorten but slightly against a heavy load, (small stroke volume and high pressure during occlusion) but can shorten considerably against a light load (large stroke volume and low pressure

after occlusion). The energy for increased work is available at each heart beat even though conditions may be such that work cannot be done.

Changes in stroke volume and in ventricular work are roughly parallel to changes in the duration of systole even though systole is corrected for cycle length or cycle length is held constant by the use of atropine. [This investigation was aided by a grant from Life Insurance Medical Research Fund.]

Modifications in the method for calculating stroke volume from the central pressure pulse contour. W. F. HAMILTON and JOHN W. REMINGTON *Dept. of Physiology, Univ. of Georgia School of Medicine, Augusta, Georgia*. In calculating the stroke volume from the contour of the central arterial pulse (*Am. J. Physiol.* 148: 14, 1947), it is necessary to estimate arteriolar drainage during systole. This was done by dividing the time-pressure area of systole by that of diastole, and multiplying the quotient by the uptake of the arterial tree. For the calculation of systolic area, the weighted average transmission time to the periphery ( $T_w$ ) was subtracted from the actual duration of systole in the central pulse, so that only drainage which had occurred before semilunar closure was measured. To the time of diastole, then, was added  $T_w$ , assigning a diastolic pressure value to the latter for area calculation.

It seems from correspondence with R. S. Alexander, and from intramural discussion, that it would be logical to give  $T_w$  time its actual pressure value, as taken from the central contour, rather than a diastolic pressure value. That is, the  $T_w$  area in late systole is added to diastole, and the  $T_w$  prolongation of diastole (area G) is omitted. This would render the total diastolic area greater, and the systolic drainage less. Recalculating our published results in this manner shows an average reduction of the stroke volume by 4.5%. Since this is within the experimental error of the dye injection technique, and in fact, lowers the average to a value closer to that from the latter technique, it would appear a valid substitute for the published procedure. The correction is most important in experiments where peripheral resistance is low.

Morphine induced secretion of pitressin in dogs with hypophyseal stalk section. CARROLL A. HANDLEY (by invitation) and A. D. KELLER *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine, Houston, Texas*. DeBodo (*J. Pharmacol.* 82: 74, 1944) has demonstrated that morphine causes the liberation of pitressin in normal dogs, but failed to find evidence for the liberation of pitressin by this agent in hypophysectomized animals. We have found that morphine in a dosage of 0.2 mg per kg, given intravenously, will result in antidiuresis of several hours' duration in dogs with mild (3000-4000 cc urine/24 hours) permanent diabetes insipidus. The urine collected



during the period of antidiuresis assayed by the sensitive method of Hare et al (Endocrinol 36 325, 1945) shows that these animals excrete 0.5 to 3 millimoles of pitressin per hour. Observation of dogs with high section of the pituitary stalk but without diabetes insipidus has yielded similar results.

These findings indicate that the liberation of pitressin by chemical stimuli is still possible after the supraopticohypophyseal tract has been severed.

**Intensity discrimination of pain sensation**  
JAMES D HARDY, HAROLD G WOLFF, and HELEN GOODELL (by invitation) *Russell Sage Inst of Pathology and the Depts of Physiology and Medicine, Cornell Univ Medical College, in affiliation with the New York Hospital*. The ability of three human subjects to discriminate small differences in intensity of painful stimuli has been investigated with the Hardy-Wolff-Goodell pain threshold apparatus<sup>1</sup>. The subject was presented with a painful stimulus and then a series of painful stimuli of greater and lesser intensities than the first "standard" stimulus. These he compared with the first stimulus, reporting whether the subsequent stimuli were of equal, greater, or lesser intensity. The difference limen was measured as the minimal intensity above and below the original stimulus which could be distinguished with certainty from it. Distinguishable differences in intensity were ascertained for a series of stimuli from the pain threshold (200 millicalories per second per cm<sup>2</sup>) to stimuli which caused blistering (450 mc/sec/cm<sup>2</sup>). For stimuli between 200 and 300 mc/sec/cm<sup>2</sup> the difference limen was constant at 7-10 mc/sec/cm<sup>2</sup>. Between 300 and 330 mc/sec/cm<sup>2</sup> there was an abrupt rise of the difference limen to 18-20 mc/sec/cm<sup>2</sup>, and this value pertained to stimuli up to 400 mc/sec/cm<sup>2</sup>. Between 400 and 450 mc/sec/cm<sup>2</sup> there was a final sharp rise in the limen and stimuli greater than 480 mc/sec/cm<sup>2</sup> could not be distinguished from each other. This suggests that pain sensation due to radiant heat has an upper limit or "ceiling" of perception for stimuli at approximately twice the threshold stimulus, beyond which further discriminations are impossible. Tissue damage occurred with these "ceiling" stimuli in every case. These subjects were able to discriminate 21 steps in the intensity of pain from threshold to the "ceiling" intensity.

**Thermoregulatory phenomena associated with exposure to warm and cold environments**  
JAMES D HARDY and HELEN GOODELL (by invitation) *Russell Sage Inst of Pathology and the Depts of Medicine and Physiology, Cornell Univ Medical College, in affiliation with the New York Hospital*. Twenty medical students were exposed for three

hours lying on an army cot in minimal clothing to a temperature of 31°C (87.8°F). During this period measurements were made of metabolic rate, rectal, and skin temperature. From these data, the average body temperature (0.8 rectal + 0.2 skin) and peripheral blood flow index<sup>1</sup> could be computed. At the end of the exposure to warmth, the students were conducted into a room at 16°-18°C (60.8°-64.4°F) and the above measurements were continued over a four hour period. In the warm environment metabolism was at or below normal standards, and peripheral blood flow index was between 200 and 600 cc/minute. Upon exposure to cold, there was a temporary rise in rectal temperature (0.3°-0.8°C) which subsided in two or three hours<sup>2</sup>. It is believed this rise is due partly to the sudden vaso-constriction associated with the strong cutaneous stimulation of the cold air. There was little or no change in the metabolism in most subjects until shivering occurred, the peripheral blood flow index decreased rapidly to minimal values. Shivering was accompanied by a temporary rise in metabolism, rise in skin temperature, rise in peripheral blood flow, and increased heat loss. Subjects appeared to be able to resist shivering during short periods immediately following a chill. This was apparently associated with the relief of feelings of intense cold brought about by the temporary rise in skin temperature.

**Hormonal influence on basal metabolism of women in cold and warm environments**  
JAMES D HARDY, EPHRAIM SHORR, and EUGENE F DuBOIS *Russell Sage Inst of Pathology and the Depts of Medicine and Physiology, Cornell Univ Medical College, in affiliation with the New York Hospital*. Metabolism experiments which were carried out in the Russell Sage Calorimeter on seven apparently normal women showed that six of the seven subjects had a lower basal metabolism (ca 13%) when measured at a calorimeter temperature of 32°C than when studied at 26°C<sup>3</sup>. It was observed that the only woman who failed to show this change was suffering from amenorrhea. Using this observation as a clue, four additional women have recently been studied in warm and cold environments. Three of the subjects were postmenopausal, one amenorrheic with anorexia nervosa, and all four women showed no change in metabolism when the temperature was changed from 31°C to 26°C. In one menopausal subject a full estrus type vaginal smear was produced by administration of estrogens. While in this phase, the subject demonstrated the change in metabolism observed in the normally menstruating young women. When

<sup>1</sup> Hardy, Wolff and Goodell, *J Clin Inv*, Vol XIX, No p 649 July 1940

<sup>2</sup> Hardy & Soderstrom, *J Nutrition*, Vol 16, No 6, 1938

<sup>3</sup> Confirming unpublished observations by R W Keeton

<sup>4</sup> Hardy, Milhorat and Du Bois, *J Nutrition*, Vol 4 p 383, 1941

studied some time later, after discontinuing estrogens and after the vaginal smears had again become menopausal, she again failed to show the change in metabolism with temperature. This evidence supports the original assumption that the change in basal metabolism observed in the normal women is dependent upon estrogenic activity.

**The nervous control of the release of pituitrin**  
**KENDRICK HARE** *Dept of Pediatrics, Cornell Univ Medical College* An elevation of the osmotic pressure of the plasma causes an increase in the rate of liberation of pituitrin from the neurohypophysis (Chambers, et al, *Amer Jour Physiol* 144: 311, 1945). The mechanism of this response has been studied in a series of 20 dogs in which the osmotic pressure of the plasma was elevated by the intravenous infusion of 2.5% NaCl solutions. The rate of pituitrin release was indicated by the chloride R/P ratio (Hare, Hare and Phillips, *Amer Jour Physiol* 140: 344, 1943). The possible mechanisms that have been investigated are:

- 1) The direct action of the osmotic stimulus upon the neurohypophysis. This possibility was rejected because transection of the pituitary stalk abolished the response although the blood supply to the pituitary remained demonstrable by the post mortem injection of India ink.

- 2) A peripheral receptor sensitive to changes in osmotic pressure whose afferent fibers entered the central nervous system over either spinal or cranial nerves. This possibility was excluded by the persistence of the response after the interruption of all nervous paths to the diencephalon. This was accomplished by transection of the midbrain, of the cervical sympathetic trunks and of cranial nerves I, II, and III. In some dogs the cerebral cortex was excised. Only the vascular channels remained as means of communication between the diencephalon and the rest of the animal.

- 3) An osmotic pressure receptor contained within the diencephalon and which influenced the activity of the hypothalamico-hypophyseal nerve fibers to regulate the release of pituitrin. This possibility has been confirmed.

**The influence of vagotomy upon ulceration of the gastric rumen of rats following pyloric ligation**  
**HENRY N. HARRIS and STUART R. ELLIOT, II** (by invitation) *Dept of Surgery, Johns Hopkins Univ, Baltimore* Ligation of the pylorus in rats starved for 48 to 72 hours leads to ulceration of the gastric rumen, as shown by Shay (1945). In the present study this procedure was done on two sets of animals: control rats, and those with coincident transabdominal vagotomy.

In the 17 control animals as compared to 15 vagotomized rats, there were respectively at the end of 24 hours: 346 and 0 small ulcers of the rumen, 37 and 0 large ulcers (over 4 mm in largest diameter), 1 and 0 perforations, ulcerations of gastric

mucosa proper in 7 and 0 rats, average of 14 and 7 cc fluid in stomach, average of 17 and 7 units of free acid in the gastric fluid, and 81 and 56 units of total acid respectively. In addition, the gastric fluid in the control rats was darker and contained more blood than in the vagotomized series. The fluid in the former animals was never frothy, in the latter it was almost always so.

The possibility that the greater distention of the stomach in the control series may have been a deciding factor is to be considered. Furthermore, some vagotomized rats allowed to live longer than 24 hours showed occasional ulcerations. However, in survival experiments, the vagotomized rat always lived longer than its paired control. The sparing effect of vagotomy on rats submitted to the Shay procedure is thus evident although its mechanism has not been exactly determined.

**The effects of anoxemic anoxia upon conduction and excitability of mammalian cardiac muscle in situ**  
**A. SIDNEY HARRIS and WILSON P. MATLOCK** (by invitation) *Dept of Physiology, Western Reserve Univ Medical School, Cleveland, Ohio* The hearts of morphine-barbital anesthetized dogs were surgically exposed. Electrograms from local leads and an Ekg were recorded simultaneously. Through mechanical controls the heart was driven at a constant rate via electrodes to the right auricle, and testing stimuli from an electronic stimulator were applied to the ventricles at any desired moment of the cardiac cycle. The oxygen concentration of inspired air was controlled by the use of an artificial respiration rebreathing apparatus.

Relative changes in conduction rate were indicated by changes in the time elapsing between the application of a ventricular stimulus and the onset of the resulting local spike recorded at a distance. As the oxygen content of inspired air was gradually reduced from 20.9 per cent (at room barometric pressure) to the range of moderate anoxia, 12 to 8.5 per cent  $O_2$ , a small diminution in stimulus response time, interpreted as increased conduction rate, usually was seen. In severe anoxia, 8 to 5 per cent  $O_2$ , there was lengthening of intervals (slowed conduction) which became very great during the dilatation and failure of the ventricles.

In some experiments there was evidence of reduced threshold to brief (3 msec) spike-like shocks during the moderately anoxic stage. In severe anoxia, with developing signs of failure, the voltage threshold rose rapidly, increasing by four or five hundred per cent within a few minutes. This dramatic reduction in excitability was confirmed with D.C. currents of 3 or 4 seconds duration. [This research was aided by a grant from the Ella Sacks Plotz Foundation.]

**Effects of anoxemic anoxia upon refractoriness of mammalian cardiac muscles in situ**  
**A. SIDNEY HARRIS and WILSON P. MATLOCK** (by invitation)

*Dept of Physiology, Western Reserve Univ, School of Medicine, Cleveland, Ohio* The hearts of morphine-barbital anesthetized dogs were exposed and the duration of refractoriness was measured during control periods and during varying degrees of oxygen lack

The heart was driven at a constant rate by shocks applied to the right auricle. Testing stimuli from a mechanically tripped electronic stimulator were applied to the ventricular muscle at the desired moment in the cardiac cycle. Test shock voltages were arbitrarily set at three times the control threshold. In a series of trials at any given oxygen level test shocks were first delivered considerably later than the end of the T wave. In each succeeding trial test shocks were delivered a few msec earlier than in the trial before. These trials continued until no further responses were evoked.

The duration of refractoriness was measured from the beginning of R(EGG) until the delivery of the shock which just failed to evoke a response or which when repeated evoked an occasional response. This shock was always in the T wave, at or later than the summit.

The results are represented by the measurements from the following experiment. Control refractory period, 204 msec, 10 per cent O<sub>2</sub>, 188 msec, 7.5 per cent O<sub>2</sub> (with falling blood pressure), 160 msec. Further testing was rendered unreliable by rising threshold and slowing A-V conduction. The findings are significant in considering the possibility of reentry phenomena and ventricular fibrillation in conditions that produce anoxia. [This research was aided by a grant from the Ella Sachs Plotz Foundation.]

**Contribution of adrenals to morphine analgesia**  
STANLEY C. HARRIS and FRANCES J. FRIEND (introduced by J. S. Gray) *Dept of Physiology and Pharmacology, Northwestern Univ Dent School and Department of Physiology, Northwestern Univ Medical School* That morphine is an efficient analgesic is established. Since it is well known that morphine administration elicits the release of epinephrine from the adrenals and since epinephrine has been shown to be analgesic, this study was undertaken to ascertain if the adrenals are involved in the production of analgesia by morphine.

The response of albino rats to tail pinching after 5 mg of morphine sulfate (subcutaneously) per kilogram of body weight was determined on 5 separate occasions before and 5 separate occasions after bilateral adrenalectomy. To protect against cortical deficiency, the cortices were autotransplanted into the anterior chamber of the eye. Medullary tissue does not "take" in this procedure. An additional control experiment consisted of the procedure before and after dummy operations. All, 240 assays were performed on 24 male rats.

In terms of distance between the prongs of the stimulating forceps, there was a 40 per cent decrease in analgesic response to the standard dose of morphine after adrenalectomy and only a 6 per cent decrease in response after the dummy operation. Statistical treatment of the data show tolerance to be of no consequence in this interpretation. [Aided in part by a grant from Smith, Kline and French Laboratories.]

**Fluctuation of response of single visual sense cells**  
H. K. HARTLINE, LORUS J. MILNE (by invitation) and I. H. WAGMAN *Johnson Research Foundation, Univ of Pennsylvania and Dept of Physiology, Jefferson Medical College* The uncertainty of response of single visual sense cells to repeated flashes of light of "constant" intensity has been studied by recording the action potentials of single fibers dissected from the optic nerve of *Lamulus*. A series of short flashes delivered to the eye at a given intensity near threshold elicits occasional responses of one or more nerve impulses, interspersed among failures to respond. Occurrence of responses in any given series is random, according to statistical tests. The frequency of occurrence of responses increases with increasing intensity of the flashes. In most dark adapted preparations, the intensity range within which frequency of responses is greater than zero and less than 100% covers approximately one logarithmic unit. This range is not measurably affected by a temperature change of 10°C. A similar uncertainty has been found for eliciting responses equal to or exceeding some fixed number of impulses greater than one, the greater this number, the narrower is the range of uncertainty.

Light adaptation raises the threshold of the sense cell, at the same time the range of uncertainty is narrowed, on a logarithmic scale of intensity. This effect is reversed by dark adaptation.

The uncertainty of response might be explained by statistical fluctuations in the number of quanta absorbed from the "constant" flash, following the explanation that has been suggested for the uncertainty of seeing by human observers. Possibility of fluctuations in sensitivity of the receptor cell and its axone, analogous to those reported for axones stimulated electrically, must also be considered.

**Observations on hypothermia and rewarming in the dog recovery from drastic reduction in body temperature**  
HANS O. HATERIUS and GEO. L. MAISON *Depts of Physiology and Pharmacology, Boston Univ Medical School* The ability of normal dogs to withstand extreme cold while relatively free of depressant anesthetic agents has been studied. Moreover, observations have been made regarding capacity for recovery following marked reduction in body temperature.

Routinely, animals were given a short acting

anesthetic (sodium pentothal, or ether), sufficient only to offset the immediate psychomotor effects of abrupt immersion in ice water. Following comparatively light induction, the experimental animals were placed in a bath at temperature ranging from 2° to 9°C. Rectal temperatures were followed, together with pulse, respiration, and electrocardiographic recordings. When either pulse or respiration had deteriorated acutely, rewarming with hot water (45°C) was instituted.

Thirteen animals subjected to the procedure outlined survived a reduction in rectal temperature to an average of 14.8°C (range 13.0–16.4°). Recovery in each instance was complete. In two animals the rectal temperature was reduced to below 15°C on two occasions. In an additional animal the rectal temperature fell to 11.8°C (pulse 5/min, respiration 2/min) before rewarming was begun. A good initial response occurred, pulse and respiration improved and shivering commenced, but death supervened suddenly at a rectal temperature of 18.2°C, with apparent heart block.

Eight animals failed to respond favorably to rewarming after cooling to an average rectal temperature of 12.2°C (range 12.0–16.6°). The cause of death in some was clearly a matter of respiratory failure, in others it was apparently attributable to heart block. [This work was supported in part by Contract W33-038 ac 14757 with the Aeromedical Laboratory, Air Materiel Command, AAF, Wright Field, Dayton, Ohio.]

**Disturbances of vestibular function produced in animals by streptomycin.** JOSEPH E. HAWKINS, JR., *Merck Inst. for Therapeutic Research, Rahway, N. J.* The chronic neurotoxic action of streptomycin on the vestibular system has been studied in 12 rabbits and 2 cats receiving very large doses of streptomycin HCl or  $\text{SO}_4$  subcutaneously (300,000 to 450,000 units per kg per day). Vestibular function was tested daily by rotating the unanesthetized animals on a turntable, horizontal nystagmus was recorded during and after rotation by registering on an ink-writing oscillograph the concomitant variations in the corneo-retinal potential picked up by two solder disc electrodes attached to the skin at the outer canthi. In both cats and in 6 of the rabbits there was a marked loss of nystagmus, beginning on the 10th to 13th day of streptomycin administration and becoming progressively more severe. Pre and post-rotational nystagmus in the rabbits was reduced or eliminated whether the eyes were open or covered, showing loss of the optokinetic as well as of the vestibular response. In the cats only the vestibular component was abolished. No recovery of the response has been observed. In 4 rabbits the reduction in nystagmus was slight, approximating that occurring in 2 normal controls rotated daily for a month. Two other rabbits died before changes in the

response occurred. Accompanying the loss of nystagmus, dramatic disturbances of posture and gait occurred in both species, indicating deficiency of all labyrinthine reflexes and possible derangement of cerebellar function. In the cats a severe loss of hearing was apparent, the nature of which is being studied by electrophysiological methods.

**Hepato- and nephrotoxic effect of glycine.** ELIZABETH CLARKE HAY, *Institut de Médecine et de Chirurgie expérimentales, Université de Montréal.* Rats injected daily with crude anterior pituitary (LAP) develop nephrosclerosis when fed a diet containing 30% casein. On investigating what amino acids could equal casein in promoting nephrosclerosis, it was found that a diet in which half of the casein was replaced by glycine was rapidly lethal. Anorexia, decreased muscle tone and convulsions have been reported with glycine. Lillie (1932) observed hepatic but not kidney damage in rats fed a 10% glycine diet for 15 days. Richter and Gold (1942) obtained renal tubular degeneration in cats after intravenous injection.

In our first experiment 10 rats were injected daily with 20 mg of LAP, and fed a diet otherwise adequate, but containing 15% glycine. All animals died within 10 days with twitching convulsions. Livers were mottled, and kidneys, prominently patterned. Extensive focal necroses were seen in all livers, and in the renal cortex of one rat together with many hyaline casts. In a second experiment, the same diet was fed for 7 days to 18 rats, half of which were injected with LAP. Macroscopically the same liver and kidney damage was evident as before in both groups. Relative kidney weights were increased enormously in LAP treated rats (controls  $489 \pm 23$  mg per 100 cm surface area, experimentals  $639 \pm 55$  mg). Marked cortical necrosis and hyaline cast formation were observed in kidneys of 3 control and 3 experimental animals of each group. The mechanism of this toxic response is unknown, but it does not appear to be influenced by anterior pituitary hormones. [Subsidized by a grant of the Sugar Research Foundation, Inc.]

**Circulatory changes in experimental pulmonary embolism.** FLORENCE W. HAYNES, THOMAS D. KINVER (by invitation), HARPER K. HELLEMS<sup>1</sup> (by invitation), and LEWIS DEXTER (by invitation). *From the Medical Clinic and the Dept. of Pathology, Peter Bent Brigham Hospital, and the Depts. of Medicine and Pathology, Harvard Medical School, Boston, Mass.* The method of venous catheterization has been used in dogs to study the pathological physiology of pulmonary embolism. Blood pressures were measured in the following vessels: femoral artery (mercury manometer), femoral vein (saline manometer), right ventricle and pulmonary artery (Hamilton manometer). All animals

<sup>1</sup> Life Insurance Medical Research Fellow.

were autopsied at the end of the experiment. Large and small emboli were used. A balloon on the end of a catheter placed in the main pulmonary artery supplying one lobe of the lung and dilated by a pressure higher than that in the pulmonary artery so as to obstruct blood flow to that lobe, produced no consistent change in the respiratory rate, pressure in the femoral and pulmonary arteries, and heart rate of anesthetized and unanesthetized dogs. In contrast, precapillary emboli (25 to 30  $\mu$  in size), produced by the slow infusion of 1 per cent lycopodium spores into the pulmonary artery to only one lobe in anesthetized animals, regularly produced an increase in respiratory rate, pulmonary arterial and right venous pressures, electrocardiographic changes, and a decrease in femoral arterial pressure, leading to death if the embolus was continued. Different animals varied considerably in the degree and time of response to lycopodium spores. Only terminally did the peripheral venous pressure rise significantly. There was a progressive fall of cardiac output. The circulatory changes accompanying embolism were not abolished by vagus section and pithing of the spinal cord. The effect of various drugs on the circulatory and respiratory disorder resulting from pulmonary embolism is being studied.

**The effect of magnesium on body temperature in the dog.** FRED C. HEACY (by invitation) and ALAN C. BURTON, *Univ. of Western Ontario, Medical School*. Although the antipyretic action of magnesium was reported in 1916, its mechanism has not been elucidated. Two well-known pharmacological peripheral actions of magnesium are vasodilation and paralysis of the neuromuscular junction. These may both contribute to depression of body temperature. It has been reported that magnesium depresses metabolism in the rat, and such an action could also contribute to temperature depression.

The effect of magnesium on temperature regulation has been investigated by intravenous injection of 1 molar magnesium chloride into unanesthetized dogs. In a dog that is regulating against heat by vasodilation and intermittent panting, magnesium causes an increase in the intensity and amount of panting so that the body temperature is depressed. In a dog that is neither panting nor shivering, magnesium causes vasodilation and panting, with the same result. In a dog that is regulating against cold by means of shivering, magnesium usually has little effect on body temperature unless the dose is large enough to cause a paralytic action. Then the prevention of shivering is followed by a fall in body temperature. Sometimes there is a transient vasodilation, and on one occasion there was panting following the injection of magnesium under such circumstances. Doses of 0.5 ml, giving blood serum levels of less than 10 mg % Mg, consistently

these effects [Carried out with the aid of a Medical Research Fellowship from the National Research Council of Canada].

**Striatal removal without previous cortical ablation.** release, disorientation, metabolic disturbance. ROBERT G. HEATH (by invitation), DAVID A. FREEDMAN (by invitation) and FRED A. METTLER. Bilateral removal of 75 per cent of the total mass of striatum in felines, without previous cortical removal produces a consistent picture. Previous studies have resulted in the description of the effects of striatal removal following cortical ablation. In order to dissociate pure striatal from the possibility of summation effects, the striatum was approached through intact cortex, either frontally or posterolaterally through the ventricle. Inevitable cortical interruption was therefore of a different nature in different experiments but the syndrome associated with bilateral removal was identical regardless of approach. Unilateral or inadequate bilateral removal produce little effect. There is release of motor activity with phasic hyperkinesia and leaping when animal is held vertically. Muscle tone is normal. The visual pathways are intact and the animal follows moving objects, but as stationary objects are approached, it obstinately pushes against them. Bizarre postural patterns are assumed indicating greater proprioceptive defect than one observes after cortical damage alone.

The animals are dull, disoriented and out of contact with their environment. Regardless of nature of sensory stimulus applied they respond only by enhanced motor activity without withdrawal from pain and approach to pleasurable stimuli. Food does not interest them. There appears to be a partial disregard of vestibular, auditory and visual stimuli.

Bilateral removal in one stage consistently results in death in 3 to 5 days. Life is prolonged if removal is performed in several stages.

Investigation of the cause of death indicates that the striatum exerts a specific influence upon metabolic function.

**The nature of the barrier to the diffusion of intradermally injected fluids.** OSCAR HECHTER, *Worcester Foundation for Experimental Biology*. To obtain information concerning the nature of the barrier to diffusion of intradermally injected fluids the spreading activity (increased diffusion as compared to a saline control) of a variety of substances has been determined in the skin of exsanguinated rabbits. The results may be summarized as follows:

(a) The dermal barrier is freely permeable to air, oxygen, nitrogen and carbon dioxide.

(b) Fat solvents (xylol, toluene, chloroform and ether) freely penetrate the barrier, thus suggesting that lipid is a component of the barrier.

(c) Alcohol and acetone spread as in (b) but

secondarily induce skin coagulation. Dilution of alcohol or acetone with water increases the coagulation rate, the area of spread is thereby limited. Tannic acid produces results similar to those obtained with alcohol.

(d) Hyaluronidase and ascorbic acid increase the diffusion of intradermally administered fluid apparently via their effect on the hyaluronic acid component of the dermal barrier.

(e) High concentrations of proteolytic enzymes (chymotrypsin, trypsin, papain and pepsin) exhibit either slight or no spreading activity. This suggests that the dermal barrier either does not contain protein or that the protein component is resistant to the above enzymes.

(f) Fluoride, evanide, ovalate, citrate, oxidizing agents, reducing agents and detergents have no direct influence on the dermal barrier.

(g) Some agents which increase capillary permeability and produce inflammation (proteolytic enzymes, 40% urea, commercial peptones and casein digest) exhibit significant spreading activity in living animals but have no spreading activity in the skin of dead rabbits. This indicates that certain types of changes associated with inflammation in skin may induce increased permeability of the dermal barrier to aqueous solutions.

**Physiological factors in neurogenic bladders.** ROBERT F. HEIMBURGER (introduced by L. W. Freeman). *The Chicago Memorial Hospital, Chicago, Illinois.* Present knowledge of the physiology of micturition fails to supply sufficient basis for anything but empirical treatment for bladders with injuries to their nerve supply. The majority of paraplegic patients now concentrated in large centers for treatment have bladders with small capacity and high detrusor tone. This group has been subjected to study in an effort to determine the elements contributing to the mechanism of evacuation in the absence of cerebral control.

Most of the patients with spinal cord injuries have had continuous bladder drainage for periods greater than six months. During this period the mucosa of the bladder has been subjected to chronic infection and the wall of the bladder has become thickened. Cystometric studies were made before and at intervals after novocaine blocks of the various portions of the nerve supply to the bladder. Detrusor tone is diminished in most instances after blocking one or more pairs of sacral nerve roots, but is not abolished by blocking all of them. Bilateral novocaine block of the second sacral motor nerve roots is more effective in decreasing detrusor tone than is block of the other pairs of nerve roots. Bilateral block of the third sacral motor nerve roots is most effective in relaxing sphincter spasm. A combination block of both pairs of second and third sacral motor roots gives the best relaxation of both the detrusor and

internal sphincter. Bilateral block of the fourth sacral motor roots relaxes the external sphincter mechanism but has little effect on the detrusor tone.

**The influence of mecholyl and histamine iontophoresis on recovery from fatigue.** F. A. HIFIL BRANDT, SARA JANF. HOUTZ (by invitation) and FLEEN NFALL DUVALI (by invitation). *Baruch Center of Physical Medicine, Medical College of Virginia.* The efficacy of drugs thought to affect peripheral circulation was evaluated by estimating their influence on recovery from fatigue. Measured work was performed by 10 healthy adult women on an improved indicating finger ergograph. Each experiment consisted of 20 "all out" efforts with a 30 to 60 second rest pause between bouts, followed by one half hour of inactivity, during which mecholyl or histamine were administered by iontophoresis or control observations were made. The latter included rest, medical galvanism, and iontophoresis with a placebo unction containing no histamine. The experiment was then repeated, and work done in the second series of 20 bouts was compared with the first.

The data consist of 10,680 ergographic fatigue curves yielding 267 paired estimates of maximal voluntary working capacity. Although the exercise was of sufficient severity to threaten the integrity of peripheral parts moving the load, and often caused a disabling synovitis, muscle soreness *per se* was never a serious complicating factor. The initial bout of 20 "all out" efforts was accompanied frequently by visible and palpable swelling of the belly of the long digital flexors. Mecholyl and histamine alone produced relief from pain, swelling and stiffness which was unequivocal, leaving the arm warm and supple. Neither increased the ability to perform work by amounts significant statistically.

**Correlation of urinary gonadotrophin titers with degree of seminiferous tubule involvement in human male sterility.** CARL G. HELLER, WARREN O. NELSON, EDWIN C. JUNCCK (by invitation) and WILLIAM O. MADDOCK (by invitation). *Dept. of Physiology and Medicine, Univ. of Oregon Medical School, Portland, Oregon and Dept. of Anatomy, Univ. of Iowa Medical School, Iowa City, Iowa.* In instances of male sterility with varying degrees of oligospermia, urinary gonadotrophin titers were found to vary from normal to as high as castrate levels. The greater the degree of hyalinization of the seminiferous tubules and the greater the number involved, the higher the titers become. Absence of germinal elements with

<sup>1</sup> Merck & Company, Inc. kindly supplied the mecholyl and Hoffman-LaRoche, Inc. provided the histamine ointment and Imadyl base used in these studies. Professor L. E. A. Kelson of the School of Engineering, University of Wisconsin devised and constructed the ergograph.

Sertoli cells remaining as the only intratubular cells, unassociated with hyalinization, was also accompanied by an elevation of gonadotrophin titers in proportion to the number of tubules involved. Failure of maturation of the germinal elements, at whatever stage it occurred and involving any number of tubules, was associated with normal gonadotrophin titers.

The effect of myocardial injury location on the S-T segment displacement. H. K. HELLERSTEIN (by invitation) and L. N. KATZ. *From the Cardiovascular Dept., Research Inst., Michael Reese Hospital, Chicago, Illinois.* Injury was produced by heat, pressure, alcohol or potassium chloride in 20 open-chested anesthetized dogs. The cavity of the heart and the endocardial and epicardial surfaces were explored with non-polarizable Ag-AgCl electrodes, the indifferent electrode being placed on the leg.

Following epicardial injury the S-T deviations were not distributed equally in all directions over the epicardium, and the time evolution of the change to oppositely directed T waves was not uniform. A positive S-T displacement was found at the site of injury. This was surrounded by a millimeter zone of non-deviation of the S-T segment. This in turn was surrounded by a zone of several cms. with downward displacement of the S-T segment. Beyond this zone, the S-T segment tended to approach the non-deviated position. When the exploring electrode was moved on to the lateral wall, the S-T remained non-deviated. When it was moved to the surface of the heart opposite that which was injured, the S-T again became depressed. When the electrode was in the cavity or on the endocardial surface, injury anywhere on the epicardial surface produced a downward directed S-T segment. Downward displacement of the S-T was also noted in epicardial leads overlying endocardial injury. Intramural injury not surfacing on the epicardium or endocardium had no external effects.

These changes can be explained by assuming that there is a polarized surface at the junction of injury with uninjured areas.

Coronary T waves often appeared later. These were oppositely directed to the earlier S-T deviations. On rare occasions such T waves preceded the development of the S-T displacement.

Nature of a principle in blood which elicits a sustained pressor response in nephrectomized animals. O. M. HELMER, R. E. SHIPLEY and K. G. KOHLSTAEDT (by invitation). *Lilly Lab for Clinical Research, Indianapolis City Hospital.* A pressor principle has been found in plasma obtained from the terminal blood of cats which have died from DDT poisoning, from hemorrhagic hypertension, or from certain "natural causes." It appears to be protein in nature, it is heat labile,

it does not pass through dialyzing or ultrafilter membranes.

The active substance is partially but not completely precipitated at pH 4.0 by saturation with sodium chloride or 0.5 saturation with ammonium sulfate. It is completely precipitated by 0.6 saturation with ammonium sulfate.

The small amount of renin present in the terminal cat plasma (as determined by its ability to make angiotonin *in vitro*) is not sufficient to account for the marked and sustained pressor action of the plasma. The injection of a fresh solution of renin (extracted from cat kidneys) which possesses an equivalent ability to make angiotonin *in vitro* does not cause the same marked or sustained pressor response in the pithed cat nephrectomized two days before.

Recovery of temperature regulatory responses after ether anesthesia. ALLAN HEMINGWAY. *The Dept. of Physiology, The Univ. of Minnesota School, Minneapolis.* In experiments on temperature regulation the physiologist is limited in his experimental preparations to the use of unanesthetized animals because anesthetics, in dosages required for surgery, depress the temperature regulating responses. Where minor surgical procedures are to be used and the temperature regulatory responses measured it is necessary to know how long the depressant effect of an anesthetic will continue after cessation of anesthesia. Most rapid recovery is to be expected with the volatile anesthetics due to their rapid elimination by respiration. Dogs were anesthetized for 30 minutes by breathing air containing 10 to 12 mgs. per 100 mls. of ether. After termination of the ether administration the temperature regulatory responses were tested after  $\frac{1}{2}$ , 1, 2 and 3 hours. The ether content of the blood, during anesthesia and during the temperature response test, was measured. The response test consisted of a standard procedure in which the animals were equilibrated in a warm environment at 35° C. for 30 minutes after which the animals were exposed to a cold environment of 8° C. The responses tested were, (1) the ability to maintain normal rectal temperature, (2) the ability to produce peripheral vasoconstriction as estimated by the skin temperature response, and (3) the ability to shiver. In 40 experiments using 4 dogs it was found that within 90 to 150 minutes after cessation of ether anesthesia the three responses had returned to normal. Shivering was least affected by ether.

Autonomic factors in the relation of EEG to heart rate. CHARLES E. HENRY (by invitation) and CHESTER W. DARROW. *Inst. for Juvenile Research, Chicago.* Study of relation of EEG to heart rate among a group of patients and normal persons varying widely with respect to age and clinical history confirms the earlier observed tendency for high



voltage slower EEG activity to be associated with fast heart rates. The majority of high voltage and slow motor and motorparietal area EEGs, including petit mal spike and wave patterns, occur in individuals having resting heart rates above 90/m. These include cases above 90/m during the fast phase of resting sinus arrhythmia. The limited number that have high voltage and slow EEGs but heart rates less than 90/m are characterized by inferior sympathetic (or central?) activity as indicated by low level palmar skin conductance (sweating) or small palmar galvanic reactivity and recovery. There are no instances of high voltage slow EEGs among individuals having resting heart rates less than 60/m. Absence of high potential slow EEGs notwithstanding heart rates above 90/m is rare save in association with blood pressure above 130 mm Hg, low conductance, or in association with strong central (?) activity as indicated by palmar galvanic reaction and recovery. Relation to age will be considered.

**Blood and plasma changes in semi-starvation and subsequent rehabilitation.** AUSTIN HENSCHKE, HENRY LONGSTREET TAYLOR, ANCEL KRIS and ANCIE MAE STURGEON (by invitation) *Lab of Physiological Hygiene, Univ of Minnesota, Minneapolis*. Blood and plasma volumes were determined by the dye dilution method (T1S24) on 32 young men during a control period, after 24 weeks of semi starvation (S24) when body weight loss was 24%, 12 weeks of controlled rehabilitation (R12), and an additional 8 weeks of recorded but uncontrolled diet (R20). Values are expressed as per cent of control. Total blood volume progressively decreased to 87.1% by R12 but returned to normal at R20 (99.2%). Expressed as cc per kg body weight, blood volume increased to 120.0% at S24, was 104.4% at R12 and decreased to 94.1% at R20 when body weight was 5% above normal. Total plasma volume in liters remained constant (3.130 at C, 3.395 at S24, 3.090 at R12 and 3.149 at R20) but in cc per kg body weight it reflected body weight changes and was 142.2% at S24, 122.7% at R12 and 95.0% at R20. Hemoglobin concentration decreased to 77.5% at S24, was 84.8% at R12 and 96.7% at R20. Total hemoglobin which is dependent on relative and absolute changes in blood and plasma volumes and hemoglobin concentration decreased to 70.9% at S24, was 73.8% at R12 and 95.9% at R20. In four subjects followed for more than a year, total hemoglobin reached control levels (99.0%) between 33 and 58 weeks of rehabilitation. Blood changes that occurred in semi starvation recovered slowly but were essentially normal after 5 to 12 months of rehabilitation.

**Experimental studies on microwaves and**

**possible applications in physical medicine** J F HERRICK, F H KRUSEN (by invitation), U M LEDEN (by invitation) and K G WAKIM *From the Division of Experimental Medicine, Section on Physical Medicine and Section on Physiology, Mayo Foundation and Mayo Clinic, Rochester, Minnesota*. For several years one of us (Dr Krusen) had been attempting to procure a microwave generator which would have sufficient output to permit possible applications in physical medicine. The development of the cavity magnetron tube has made such a microwave generator a reality. Through the generosity of the Raytheon Manufacturing Company, microwave equipment has been procured. At present we are studying the heating effects of microwaves which have a frequency of 3,000 megacycles per second. Our studies, thus far, have been concerned chiefly with observations on the changes in temperature of certain bodily sites such as the skin, subcutaneous tissue and muscle tissue in the thigh and thorax. It is possible, by the use of microwaves, to raise the temperature several degrees in skin, subcutaneous tissues and muscle tissues. No changes in rectal temperature were observed unless the animal was anesthetized.

Since the production of heat in bodily tissues is one of the most desired therapeutic procedures in physical medicine, the application of microwaves may prove to be of value to the physiatrist.

The equipment and its application will be described and representative data will be given.

**Renal clearance of citrate in dogs** R C HERRIN and C C LARDINOIS (by invitation) *Dept of Physiology, Univ of Wisconsin Medical School, Madison*. In 5 of 6 dogs the endogenous citric acid renal clearance averaged less than 1.5 ml. The ratio of citric acid clearance to that of creatinine was less than 0.03. In the sixth dog, the clearance averaged 8.2 ml and the ratio of clearances averaged 0.118. The oral administration of citric acid to 4 dogs in doses of 6 to 10 gms, in 2 experiments had no significant effect on the citric acid clearance and in 5 it resulted in a 3 to 25 fold increase. The administration of sodium or potassium bicarbonate was tried on 5 dogs. In every case it markedly increased the ratio of the citric acid clearance to the creatinine clearance, indicating less tubular absorption of the citric acid. In 18, alkali administration resulted in a marked increase in the citric acid clearance. In 6 cases the plasma citrate increased markedly but in the others no significant change occurred. Following sodium bicarbonate administration, the increase in urinary citric acid in milliequivalents per liter over a period of hours was only a small fraction of the increased quantity of sodium excreted. It was noted in these experiments, regardless of the procedure, when the plasma citrate significantly in-

<sup>1</sup> Sponsorship for this work will be acknowledged in final publication.



creased, as it did in 17 cases, the citrate Tm always increased. When plasma citrate did not rise, the Tm either remained the same or decreased.

**Estimation of cutaneous blood flow with the photoelectric plethysmograph in the presence of arterial pathology.** A. B. HERTZMAN and W. C. RANDALL. *From the Dept of Physiology, St. Louis Univ. School of Medicine, St. Louis, Mo.* An approximately linear relation appears to exist between the cutaneous blood flow and the amplitude of the photoelectrically recorded skin pulses in the finger pad of the normal subject (Amer J Physiol 145:716, 1946).

Two lines of experimental evidence may be cited to support the argument that this relation obtains also in the presence of hypertension, diminished elasticity of the arteries and occlusive arterial diseases.

1 *Qualitative directional agreement* with other qualitative criteria of cutaneous blood supply (skin temperature, skin color, capillary blood flow, arterial pressure gradients, oscillometric index, arteriography, etc.) is regularly exhibited in patients with peripheral vascular diseases when "resting" and when subjected to various constrictor and dilator influences (thermal, "psychic", sympathetic block, local histamine or mecholyl, tetra-ethyl ammonium chloride, etc.).

2 The correlation between photoelectric and calorimetric estimates of finger pad flows was examined in a series of hypertensive and arteriosclerotic patients during thermal reflex dilatation. The flow equivalents of the photoelectrically recorded skin pulses thus estimated were distributed within a range so near normal that no specific effect on them could be attributed to altered arterial dynamics (as indicated by pressure gradients) or pathology. Errors inherent in the calibration procedure appear to mask a possible influence of arterial pathology on the flow equivalents. [Aided by a grant from the United States Public Health Service.]

**The conversion of cyanide to thiocyanate by tissues.** W. A. HIMWICH and J. P. SAUNDERS (introduced by Harold E. Himwich). *Toxicology Section, Medical Division, Edgewood Arsenal, Md.* The ability of various tissues of the dog and the monkey to convert  $-CN$  to  $-CNS$  *in vitro* was studied. Tissues were homogenized in 10 volumes of distilled water for five minutes in a Waring blender and filtered through several thicknesses of surgical gauze. An aliquot of the homogenate was added to a system containing phosphate buffer pH 7.6, potassium cyanide, 0.014M, and sodium thiosulfate, 0.042M. The mixture was shaken in a water bath at 38°C for fifteen minutes. Thiocyanate was determined colorimetrically, using ferric nitrate. The thiocyanate formed by the re-

agents in the absence of tissue and the amount originally present in the tissue were determined.

In terms of the ability of one gram of tissue to produce thiocyanate from cyanide, the tissues of the dog rank in the following order: suprarenals, liver, caudate nucleus, cerebral cortex, kidney, testis, medulla, cerebellum, spinal cord, pancreas, heart, small intestine, spleen, muscle, whole blood, erythrocytes, and plasma. Although in the monkey the tissues rank in somewhat different order, the primate is able to detoxify 100-200 times as much cyanide as the dog. In both species thio sulfate is necessary for the conversion.

Further studies are being made on the enzyme mechanisms involved as well as on the detoxifying ability of tissues from other species.

**The response of normal dogs to explosive decompression to 30 mm of Hg.** FRED A. HITCHCOCK and ABRAHAM EDELMANN (by invitation). *Dept of Physiology, the Ohio State Univ., Columbus.* A series of dogs have been explosively decompressed to 30 mm Hg and kept at this pressure for from 15 to 120 seconds. The sequence of events following the explosion was as follows: respiration became deep and rapid, abdominal distension occurred, animals collapsed, mild convulsions occurred, animals became quiescent except for occasional gasping movements, lacrimation, salivation and urination occurred. All visible respiratory movements ceased about 30 seconds after the explosive decompression. Shortly after this, subcutaneous swelling started in the lower abdomen and progressed headward. Thirty to thirty-five seconds after the explosion the eyes were glazed and the animal appeared to be dead, and remained in this condition until recompression. When the animals were recompressed to about 55 mm the distension of the body decreased, and at 100 mm the dogs were almost back to normal size. When normal barometric pressure was reached and the chamber opened the animals had invariably ceased breathing but the heart was still beating. Respiration reappeared within 30 seconds after return to atmospheric pressure. Corneal reflexes returned 3 to 7 minutes later. Several dogs kept at terminal pressure for one minute or longer showed decerebrate rigidity. This developed about 6 minutes after the explosion and lasted for about 3 minutes. The dogs were usually on their feet 12 to 13 minutes after the explosion, and 20 minutes after return to normal barometric pressure they were normal. It is believed that all effects except the swelling of the body are due to acute anoxia.

**The electrical activity of single motor units in human poliomyelitis.** ROBERT HODES JOHNSON. *Foundation and Dept of Physical Medicine, Univ of Pennsylvania.* Electromyograms of motor units of poliomyelitis patients differed so markedly from normal that several tests were performed to es-

establish their unit character. Such evidence indicates (1) A critical threshold exists for activation of these units by percutaneous nerve stimulation. When threshold is reached the unit responds maximally, or not at all. (2) Potentials evoked voluntarily or reflexly are identical in amplitude and duration with those produced by stimulation of the motor nerve close to the muscle. Such lack of temporal dispersion with conduction distances differing by more than a meter is unlikely if more than one motoneuron were active.

In poliomyelitis the motor unit potentials diminish progressively in amplitude during brief voluntary effort or tetanic nerve excitation, but the duration of the spikes is unchanged. The voltage reduction results from failure of some muscle fibers of the unit to respond to each nerve impulse. This failure is caused by a block at the neuromyal junction produced by the disease processes. The constant spike duration implies that the component muscle fibers of the unit are activated practically simultaneously, with no significant temporal dispersion.

The conduction velocities of the nerve fibers supplying the motor units examined were 31-32 meters per second—approximately half the conduction rate of the largest fibers to the corresponding normal muscles, and about one quarter that of the fastest known skeletal motor fibers of animals and man.

**Relationship between gastric potential and secretion when dilute saline is placed in contact with mucosa.** LOWELL E. HOKIN (by invitation) and WARREN S. REHM, *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.*

Previous studies have demonstrated that when 0.9% saline is placed in contact with the mucosa of the secreting stomach, the potential difference across the stomach is in the neighborhood of 40 mv (the serosa is positive in the external circuit to the mucosa). A close correlation was found between the rate of secretion of HCl and the potential when agents that lowered the potential were applied to the stomach. Using the same method (Rehm and Hokin, *Am. J. Physiol.* in press) an apparent exception to this correlation was found when normal saline was replaced with a more dilute saline. In a typical experiment the potential dropped from 40 mv to approximately 20 mv when 0.9% saline was replaced with 0.09% saline, while there was no significant change in the secretory rate. When a saline solution of an intermediate concentration was used in the place of the 0.09% saline, a smaller decrease in the potential resulted. The potential showed an immediate drop when dilute saline replaced normal saline and an immediate rise on replacing the dilute saline with the normal saline. The diffusion potentials between 0.16 N HCl and the saline solutions were measured.

The diffusion potential between 0.16 N HCl and 0.9% saline was about 30 mv, while that between 0.16 N HCl and 0.09% saline was about 60 mv. It appears from these data (see discussion in above reference) that the decrease in potential, when dilute saline replaces normal saline, is due to an increase in the diffusion potential between gastric juice and saline.

**Diffusion of painful stimuli over segmental, infrasegmental and suprasegmental levels of the spinal cord.** THOMAS J. HOLBROOK (by invitation) and C. G. DE GUTIERREZ MAHONEY, *Neurological Division, St. Vincent's Hospital, New York City.* A 29 year old man suffering from sarcoma of the right thigh muscles was studied for three months after division of the left anterolateral tract at Th<sub>2</sub> and for two months after division of the right anterolateral tract at Th<sub>3</sub>. The levels of analgesia and thermesthesia were Th<sub>5</sub>, right, and Th<sub>5</sub>, left.

After the first operation, pressure over the tumor mass and active or passive movements of the right thigh produced pain in the left testicle. Painful stimulation of the analgesic right side of the body caused a peculiar painful sensation localized exactly to a corresponding point on the left side of the body and pain in the left testicle. These phenomena were not influenced by a left lumbar sympathetic novocaine block nor by novocaine infiltration of the skin of the left abdominal wall.

After the second operation, the crossed mirror image sensations on stimulating the right side, were not experienced in the analgesic area on the left side but persisted above Th<sub>3</sub>. Painful (pin prick or pinch) stimuli over the analgesic left thigh and abdomen caused pain in the left abdominal area of dermatomes Th<sub>4</sub>-Th<sub>5</sub>. Stimuli over the medial part of the thigh were referred to the medial abdominal area and those over the lateral thigh to the lateral abdomen.

This is evidence not only for the segmental but also for infra- and suprasegmental participation in the perception and localization of noxious stimuli.

**Factors influencing the susceptibility of rats to barbiturates.** E. HOMBURGER (by invitation), B. ERSTEY (by invitation) and H. E. HIMWICH, *Albany Medical College, Albany, New York, and Medical Division, Edgewood Arsenal, Maryland.* In a study of effects of various factors influencing the susceptibility to barbiturates it was found that the age and weight, sex and strain of the rats cause significant differences. The newborn rat is more susceptible than the adult to pentobarbital while 50-200 gram rats are less susceptible than are 201-500 gram rats. Male and female rats do not necessarily respond the same way. As growth proceeds the first increase in the greater susceptibility of the female is observed in rats weighing 101-200 grams for the female remains anesthetized longer than the male. In rats weighing 201-500 grams

and receiving pentobarbital not only is the duration of narcosis longer in the female but the toxicity is greater. But the effects also vary with the kind of barbiturate, for example, though an intravenous injection either of pentobarbital or *n*-Methyl pentobarbital produces more pronounced effects in the female than in the male, pentobarbital elicits no sexual difference. The three strains of rats used in this study exhibited quantitative differences in assay of the LD<sub>50</sub> dose.

The cytochrome c-azide complex B L HOR-ECKER (by invitation) and J N STANNARD *National Inst of Health, Bethesda, Maryland* Ferriocytochrome c combines with azide to form a well-defined but highly dissociated complex. The absorption maximum is shifted from 5300 Å to 5400 Å, with the appearance of a faint new band at about 5750 Å. The band at 6925 Å, which may be observed with concentrated solutions of ferriocytochrome c, is absent in the azide complex.

From the effect of increasing concentration of azide on the absorption at selected wave-lengths, the dissociation constant of the azide-ferriocytochrome c complex is calculated to be 0.18 at 27°C. The dissociation constant is independent of pH when computed on the basis of the concentration of N<sub>3</sub> and each molecule of ferriocytochrome c combines with one N<sub>3</sub> ion. No evidence could be obtained for the existence of a complex of azide with ferrocytochrome c.

The azide complex differs in several respects from that formed with cyanide. The dissociation constant is approximately 10<sup>6</sup> times larger, but equilibrium is reached almost instantaneously, compared to the sluggish rate of formation of the cyanide complex. At the concentrations normally required to inhibit oxygen consumption, azide has no effect on the enzymatic reduction of cytochrome c, while the cyanide-ferriocytochrome c complex, once formed, is not reducible enzymatically. These observations are consistent with previously established differences in the action of azide and cyanide on cellular respiration.

Renal hyperemia in the dog after intravenous infusion of adenosine, adenylic acid, or adenosinetriphosphate C RILEY HOUCK, RICHARD J BING, FRANK N CRAIG, and FRANK E VISSCHER (introduced by Homer W Smith) *Physiology Dept, New York University College of Medicine* The effects of infusion of yeast or muscle adenylic acid upon effective renal plasma flow (p aminohippuric acid clearance) and glomerular filtration rate (creatinine clearance) in unanesthetized female dogs fall into two phases, (1) the infusion, and (2) post-infusion. The first consists of a reduction in filtration rate ranging from 10 to 100 per cent, depending upon the degree of reduction in blood pressure (femoral artery puncture, mercury manometer). If filtration is between 50 and

100 per cent of normal, renal plasma flow remains constant or increases to as much as 155 per cent of normal. However, if filtration drops below 50 per cent of normal, plasma flow also decreases, to zero in some instances. In every case, the filtration fraction decreases. It is concluded that a combination of general arteriolar dilatation, afferent arteriolar constriction and efferent arteriolar dilatation occurs.

The post-infusion phase begins immediately after stopping the acid infusion and consists of an immediate return of blood pressure and filtration rate to or near normal, and, in every instance, a hyperemia, ranging from 111 to 168 per cent of normal and lasting for as long as 45 minutes. Consequently, the filtration fraction remains reduced, indicating dilatation principally of the efferent arteriole and, to some degree, of the afferent arteriole.

Qualitatively similar results are obtainable with muscle or yeast adenosine or sodium adenosinetriphosphate.

A poor correlation exists between the above alterations of renal functions and the rate of infusion or total amount of the particular compound infused.

Mechanism of death in dogs following the intravenous injection of nitrogen mustards C RILEY HOUCK (by invitation), BETTI CRAWFORD (by invitation), JAMES H BANNON (by invitation) and HOMER W SMITH *Dept of Physiology, New York Univ College of Medicine* One hundred and fourteen dogs were intoxicated by the intravenous injection of 1.0 mg/kg of the hydrochloride of methyl-bis(β-chloroethyl)amine (LD<sub>50</sub>) or bis(β-chloroethyl)amine (LD<sub>75</sub>). Excluding a few animals with severe pulmonary injury, it is inferred that death on the third to fifth day is caused by anoxia of the respiratory centers as a consequence of peripheral circulatory failure precipitated chiefly by a reduction in blood volume attributable to loss of proteins, electrolytes, and water through profuse vomiting and diarrhea, supplemented by loss of red cells through intestinal hemorrhage or as yet unidentified channels. Such changes are revealed in the following data at 72 hours after intoxication: reduction in plasma volume and total circulating protein with an increase in protein concentration, variable reduction in total circulating red cell volume, reduction in plasma chloride concentration, and a variable increase in carbon dioxide capacity, blood pH and hemoglobin concentration or oxygen capacity. Terminally, low arterial blood pressure, reduced renal blood flow (p aminohippuric acid clearance) and, correspondingly, filtration rate (creatinine clearance), marked oxygen unsaturation of jugular blood (with presumably normal arterial saturation), and reduction in body temperature are

associated with weakness and coma preceding death. Two procedures (1) replacement of fluid, electrolyte, and protein by various methods and (2) protection of the small intestine from the toxic agent by occlusion of its circulation during and for 15 minutes after injection of the agent prolonged survival without affecting ultimate mortality. [Work done under contract with O S R D]

**Acclimatization to extreme cold** STEVEN M HORVATH, A FRIEDMAN (by invitation) and H GOLDEN (by invitation) *Armored Medical Research Lab., Fort Knox, Kentucky*. Metabolic observations were made on five subjects who resided continuously for three days in a comfortable environment, 25°C, for eight days in a cold environment, -29°C, and for another three day period at 25°C. No changes in basal values for heart rate or rectal temperature occurred. The caloric expenditures during quiet sitting and while performing a standard amount of work were higher during exposure to the low ambient temperature. The duration of exposure to low temperatures did not markedly influence the energy output during the sitting period for four of the five subjects. The fifth individual, who was breathing air of approximately 20°C during this time, showed a striking decrease in caloric output with increased exposure. The significance of this finding and its association with a higher level of toe temperature has been discussed. Four of the subjects exhibited an increased metabolic rate—an after stimulating effect of cold—on their return to the control environment. This was not observed in the fifth subject, the same individual mentioned above.

The energy requirements for the standard work on a treadmill at 3.0 mph and a 3.3 per cent grade were increased during low temperature exposure. A small but definite trend towards normal values occurred with continued exposure, but its relation to the development of a state of acclimatization was not clear. The decrease could be explained adequately on the participation of a number of other factors.

There is some indication from the data accumulated in this study that acclimatization to cold may occur, but at the present the evidence is too equivocal for a definite statement.

**The effect of dietary factors on the adrenal X zone** EVELYN HOWARD *Dept of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore, Md*. Since the adrenal X zone does not secrete physiologically appreciable amounts of androgen, attention is directed to another possible role for this transitory differentiation of the adrenal cortex. Preliminary data indicate that unilateral adrenalectomy in young female mice results in a reduction in the ratio of the X zone to the permanent cortex in the remaining gland.

The effect on the adrenal of three diets high in carbohydrate, protein, or fat, respectively, is under investigation. It has been found that, in young female mice, the high protein and high fat diets cause a statistically significant reduction in adrenal weights relative to that found in animals on the high carbohydrate diet. The weight reduction is correlated with a decrease in the amount of the X zone. This raises the question as to whether there is a specific relationship between X zone development and the metabolism of a high carbohydrate diet, or whether the X zone reduction with the high protein and high fat diets is a non specific result of metabolic stress set up by these diets. The larger X zone on the high carbohydrate diet might be a response to a need for the conversion of carbohydrate to fat on this diet. That certain cortical steroids augment fat formation has been indicated by Kendall. The X zone might thus be a factor in the characteristic fat deposition of female and castrated male mice, and of the human fetus.

**The nervous control of the esophagus** K HWANG (by invitation), M I GROSSMAN and A C LEE *Dept of Physiology, Univ of Illinois College of Medicine*. It has been shown (K Hwang, H E Essex, F C Mann, Am J Physiol, in press) that complete severance of both vagi just posterior to the larynx in dogs resulted in paralysis confined to the lower two-thirds of the esophagus. This is contrary to the general conception that the cervical portion of the esophagus is innervated by the recurrent laryngeal nerve.

The present studies comprising acute experiments on nine dogs under light ether anesthesia were undertaken to determine the motor innervation of the upper esophagus. Consistent results were obtained. Stimulation of the peripheral end of the vagus on either side in the neck caused an immediate tetanic contraction of the whole thoracic portion of the esophagus, but the cervical portion remained flaccid and was only pulled downward by the shortening of the thoracic part. A nerve about one third the size of the superior laryngeal nerve was found arising from the vagus nerve above the nodose ganglion passing medially and posteriorly dorsal to the superior laryngeal nerve. On the lateral surface of the inferior constrictor muscle of the pharynx it passes posteriorly as a zigzag trunk to the lateral surface of the esophagus where it breaks up into a few extremely fine branches. Stimulation of the peripheral end of the cut nerve produced strong tetanic contraction of the inferior constrictor of the pharynx as well as the whole cervical portion of the esophagus. Simultaneous stimulation of the peripheral ends of this and the vagus resulted in strong contraction of the whole esophagus.

Acetylcholine, cholinesterase, eserine and

**convulsions** JANE HYDE (by invitation), SIBYL BECKETT (by invitation) and ERNST GELLHORN *Laby of Neurophysiology, Univ of Minnesota* I Acetylcholine (AcCh) content of the central nervous system in convulsions Free and bound AcCh was assayed on the isolated Venus heart Electrically induced convulsions fail to alter the AcCh content in either fraction in eserinizated rats However, strychninized frogs show an increased AcCh content in brain and spinal cord, especially in the free fraction (see Cortell, Feldman, and Gellhorn, 1941)

II Cholinesterase and convulsive cortical potentials in the cat It is shown that the development of convulsive potentials induced by local application of strychnine, metrazol or picrotoxin is either delayed or prevented by pretreatment of the cortical area with ChE Pretreatment of the cortex with eserine potentiates the convulsant effect of the above mentioned drugs These actions are reversible and indicate that AcCh plays an important part in the causation of convulsive potentials [Aided by a grant from the U S Navy, Office of Naval Research]

**Effect of adrenal cortex extract on glucose tolerance in eviscerated rats** D J INGLE, M C PRESTRUD (by invitation) and M H KUIZENGA (by invitation) *Research Labys, The Upjohn Company, Kalamazoo, Michigan* Male rats (185-200 gm) of the Sprague-Dawley strain were caused to develop a collateral circulation by ligation of the inferior vena cava At a weight of  $250 \pm 2$  grams the animals were anesthetized (cyclopal), and all of the intra-abdominal organs were removed except the kidneys and adrenals Infusions into the saphenous vein were made by continuous injection machines which delivered fluid at the rate of 20 cc in 24 hours per rat The change in the level of blood glucose during the subsequent 24 hours was the index of glucose tolerance

In experiment 1, insulin (4 units crystalline zinc, Lilly) was added to the infusion solution of glucose and saline for all animals When large amounts of adrenal cortex extract were added to the infusion fluid, the tolerance for glucose was significantly depressed below that of the controls Hyperglycemia developed and some glucose was excreted into the urine It cannot yet be concluded that the adrenal cortical hormones were responsible for this "anti-insulin" effect, since the presence of traces of epinephrine in the adrenal cortex extracts was not controlled

In experiment 2, the study was repeated on animals not given insulin The effect of adrenal cortex extract upon the tolerance of these animals for glucose was either absent or questionable Our results indicate, but do not prove, that the presence of insulin is required for an effect of

adrenal cortex extract upon the glucose tolerance of the eviscerated rat

**The treatment of impending hemorrhagic shock by means of pentobarbital sedation** RAYMOND C INGRAHAM, FRANK ROEMHILD (by invitation), HAROLD GOLDBERG (by invitation) and HAROLD C WIGGERS *College of Medicine, Univ of Illinois, Chicago, Illinois* It has been demonstrated, by previous studies in this laboratory as well as by other investigators, that the careful administration of a proper anesthetic agent to animals in *impending hemorrhagic shock* does not unfavorably affect the subsequent transition into the *irreversible* state but may be of some benefit

Dogs subjected to a modified shock producing procedure (90 minutes of hemorrhagic-hypotension at 35-38 mm of Hg), without any treatment, enter *irreversible shock* in 70 per cent of the cases studied (20 animals) with a median post-reinfusion survival time of 11 hours

In the present experimental series of 20 dogs, sodium pentobarbital was administered in small quantities (7 mg/kg) in the middle of the 90 minute period of hemorrhagic-hypotension at 35-38 mm of Hg The mortality rate in these animals was significantly reduced (20 per cent) and the median post-reinfusion survival time among the few fatalities was 7 hours The beneficial effects of pentobarbital sedation is likewise reflected in the augmented bleeding volumes required to establish and maintain the prescribed level of hypotension

The conclusion is reached that small sedative doses of sodium pentobarbital administered during *impending shock* before the transition to *irreversible shock*, exerts a distinctly beneficial effect in delaying the onset of *irreversible hemorrhagic shock*

**Apparatus for complete recording of respiratory exchange of man** LAURENCE IRVING, P F SCHOLANDER (by invitation) and OTTO HEBEL (by invitation) *Edward Martin Biological Laby, Swarthmore College* The apparatus gives a continuous quantitative ink recording of tidal volumes, the volume difference between oxygen intake and carbon dioxide production and the total volume of carbon dioxide produced per minute and the total volume of ventilation per minute

From these curves the oxygen consumption, the respiratory quotient and the expiratory concentration of carbon dioxide and the utilization percentage of oxygen are calculated The apparatus will handle from basal to maximal respiratory exchange in man

**Principle** The expiratory gas is led to the bottom of a thermostabilized cylinder through a gas dispersing device The expired gas thereby layers in the cylinder under the air which is inspired via a spirometer This part therefore essentially pro

vides a closed circuit of breathing where no absorption and no rebreathing take place. The spirometer of this circuit records the respiratory difference curve (i.e.,  $O_2-CO_2$ ). Before the expiratory gas reaches the top of the cylinder respiration is switched over to a second layering cylinder. By the same switch the first cylinder connects with an absorption circuit, having a spirometer which records the volume of  $CO_2$  absorbed. When absorption is finished the oxygen utilized is restored to the system. By means of two layering cylinders which may alternately be connected with the respiration and the absorption circuits continuous recording of the respiratory difference curve as well as the carbon dioxide output is obtained. The ventilation is recorded by means of a mechanical device which summates all expiratory or inspiratory volumes.

**The relation between intracranial pressure and positive pressure breathing.** JOHN H. ILLI, (by invitation), FORREST E. SNAPP (by invitation) and HARRY F. ADLER. This work was initiated in order to determine any possible detrimental effects that positive pressure breathing might have on patients with an increased intracranial pressure. In order to attempt to accomplish this, a cannula was placed into the subdural space through a parietal trephine hole and attached to a saline manometer. Pressure breathing was administered with a General Electric Pneumolator at 7 inches of water pressure and with a Burn's Resuscitator at 20 cm of water pressure. It was found that in 11 dogs under nembutal anesthesia, pressure breathing as described above caused no further increase of an initial intracranial pressure of from 130 to 150 mm of saline. Pressure breathing associated with an increased intracranial pressure did, however, increase the fluctuations with respiration in the intracranial pressure in 45% of 49 instances. These fluctuations varied up to 35 mm of saline. The effect of an increased intracranial pressure on the blood arterial oxygen saturation and the possible beneficial effects of pressure breathing in raising a lowered blood arterial oxygen saturation were also studied. From 16 trials, an increase in intracranial pressure was associated with a decrease in blood arterial oxygen saturation in 10 trials, an increase in 5 trials, and no change in 1 trial. In any case it would seem that oxygen would be indicated as a matter of precaution and that pressure breathing with oxygen when indicated would not be detrimental.

**Angiopathic effect of renal insufficiency.** BENJAMIN JABLONIS (introduced by Otis M. Cope). Goldwater Memorial Hospital & New York Medical College, Flower & Fifth Ave., Hosp., N. Y. C. Renal insufficiency of varying degrees with hypertension has been produced by wrapping the animal kidneys in silk or cellophane, and replacing

them in the peritoneal cavity. With marked perinephritis, malignant hypertensive states with extensive vascular lesions have been reproduced. Studies on the effect of subcutaneous explantation of cellophane wrapped kidneys of white rats were begun by the author in 1940. The kidneys of control animals were explanted without cellophane wrapping. Simple renal explantation was extensively studied by Allen and others including the author. Animals support this type of renal locality transfer without damage to kidney function, blood pressure or body tissue, if compression of the kidney pedicle is avoided. A fibrosis develops in and around the cellophane wrapped explanted kidney, which interferes with its blood flow, and after several weeks vascular changes are present in the contralateral kidney and the myocardium. In the explanted kidney the capsule is thickened, surrounded by muscle tissue bundles, parenchyma shows areas of perivascular lymphocytic infiltration, areas replaced by masses of fibrous tissue with calcific deposits, and some dilated capsular spaces. Renal pelvis shows hyperplasia and mucous membrane epidermization. Contralateral kidney shows congestion and small perivascular lymphocytic foci. Heart shows similar areas with an occasional thickened arteriole and small areas of necrosis. Control animals showed none of these changes described above, even when sacrificed six months after unilateral subcutaneous explantation of the unwrapped kidney.

**The influence of relaxation upon the blood pressure in "essential hypertension."** EDMUND JACOBSON. *Laby for Clinical Physiology*. In previous investigations on normal and hypertensive subjects, the blood pressure was often found to vary directly but not proportionally with the action potentials in skeletal muscles, measured photographically or by the integrating myovoltmeter. The extent of the fall seemed to depend upon diminution of contraction in particular regions and in the general musculature. This suggested that whatever additional etiology may be prerequisite in "essential hypertension," the high blood pressure can result, in part at least, from habitual activity of skeletal musculature.<sup>11</sup>

Methods for the cultivation of habitual relaxation in man have been described.<sup>2</sup> Action potential studies support the assumption that patients with "essential hypertension," like normal individuals, can be trained to relax. During the past seventeen years, these procedures have been employed in the study of more than one hundred individuals who exhibited chronic vascular hypertension. During the training period of one to

<sup>1</sup> Am J Physiol 126:546, 1939. Rev. Sci. Instruments, Vol.

11 No. 12, 415, 1940. Arch. Phys. Ther. 21:645, 1940.

Progressive Relaxation. Univ. of Chicago Press, 1938.

two years or more, the blood pressure range was recorded as frequently as proved possible—in many instances bi-weekly. Variations in attendance and in other particulars make it seem clearer to present the findings individually rather than statistically.

Examination of individual blood pressure curves on the whole supports the view that chronic high blood pressure (in the absence of organic disease) can commonly result, in part at least, from excessive efforts in daily life and that the cultivation of a more relaxed state can tend in the opposite direction. The relationship of these effects in man to those demonstrable in "experimental renal hypertension" in animals remains unknown.

**Factors influencing pulse volume in models of the circulatory system** KENNETH E JOACHIM and JOHN F McDONNELL (by invitation) *Dept of Physiology, Univ of Kansas, Lawrence*. It has been shown (Fed Proc 5 52, 1946) mathematically and experimentally that, in a much simplified model of the circulatory system, the ratio  $R = \frac{\text{pulse volume}}{\text{stroke volume}}$  depends only on the product of the heart rate, peripheral resistance, and the reciprocal of the slope of the pressure-volume curve of the elastic "arterial" system. The maximum limiting value of  $R$ , in this simplified model, is 0.551.

When the model is complicated by making ejection and "diastole" unequal in duration, as in the animal, it is shown analytically that  $R$  depends not only on the product mentioned above, but also on the ratio  $\beta = \frac{\text{duration of "diastole"}}{\text{duration of ejection}}$ . In general,  $R$  becomes larger as  $\beta$  increases, when  $\beta = 2$ , the maximum limit of  $R$  is 0.689. This limit approaches 0.216 as  $\beta \rightarrow 0$ , and approaches 1.0 as  $\beta \rightarrow \infty$ .

In the original analysis referred to above, the ejection velocity curve from the pump representing the heart was a sine function of time. Experimentally recorded ejection velocity curves from the pulmonary artery of a dog are presented and compared in shape with a sine function. The effect of the shape of the ejection curve on the ratio  $R$  is discussed analytically. [Aided by a grant from the United States Public Health Service.]

**Some effects of  $\alpha$ -tocopheryl phosphate on enzymatic activity** HERBERT P JACOBI (by invitation), JAMES W CHAPPELL (by invitation) and SERGIUS MORGULIS *Univ of Nebraska, College of Medicine*.  $\alpha$ -Tocopheryl phosphate markedly inhibits the succinoxidase system. The effect is largely due to the inhibition exerted on cytochrome c, although succindhydrogenase is also inhibited but to a smaller degree.

$\alpha$ -Tocopheryl phosphate reverses the stimulating action of "Kochisalt" on the oxygen con-

sumption of muscle mince. It also inhibits the activity of liver acid phosphatase, and this effect can be partly reversed with calcium.

**Observations on the antihemolytic action of sucrose** M H JACOBS and MARIAN WILLIS (by invitation) *Dept of Physiology, Univ of Pennsylvania*. In pure hypotonic solutions of sucrose hemolysis occurs less readily than in solutions of NaCl of the same osmotic pressure. Further evidence is given that this apparently protective effect of sucrose is osmotic in nature, resulting from an exchange of osmotically active anions from the cell for OH ions from the solution which by neutralization become osmotically ineffective.

In the so called colloid-osmotic hemolysis of Wilbrandt, in which an increased permeability of the cell to cations is believed to induce hemolytic osmotic swelling, the antihemolytic effect of sucrose is evident at such low concentrations as at first sight to suggest some non-osmotic mode of action. It is shown, however, by a consideration of the theoretical ionic equilibria in such systems that a purely osmotic mechanism might account for the observed results.

The essentially osmotic nature of hemolysis by *n*-butyl alcohol and of its inhibition by sucrose is indicated by the volume changes of erythrocytes in solutions, isosmotic with blood, containing different combinations of these substances and NaCl. In pure solutions of NaCl butyl alcohol causes only swelling, in pure solutions of sucrose and in many mixtures of sucrose and NaCl it may cause rapid shrinkage followed by slower swelling as the cell becomes progressively more permeable to sucrose. By a proper exposure to butyl alcohol in a salt solution followed by dilution with an isosmotic sucrose solution erythrocytes can be obtained which for a considerable time behave as if they were freely permeable to NaCl but impermeable to sucrose.

**Thiamine deficiency in adult normal and diabetic rats as studied under paired-feeding conditions**<sup>1</sup> R G JANES and J M BRADY (introduced by W R Ingram) *Dept of Anatomy, College of Medicine, State Univ of Iowa*. Six normal rats were given a diet deficient in thiamine while six pair-fed controls received a diet containing adequate B<sub>1</sub>. Anorexia was first noted 12 days after the deficiency diet was started. The B<sub>1</sub> deficient rats lost weight more rapidly than the controls and at the conclusion of the experiment had lost 44% of maximum body weight while the controls lost 37%. Although no acetonuria was noted, the urine output increased in both pair-fed and B<sub>1</sub> deficient animals following reduced food intake. Blood sugar levels varied but followed a similar

<sup>1</sup> This work was supported in part by the Hoffmann-La Roche Co., Nutley, New Jersey.



pattern in both groups. It was assumed that death or a moribund condition could be attributed to starvation rather than polyneuritis because the mortality of the pair fed controls was as great as in the B<sub>1</sub> deficient animals. Observations on organ weights (mg/100 gm) showed that the kidneys and adrenals of the deficient animals were heavier than those of the controls. The thyroids, pituitaries and testes had similar weights. No marked pathology was found in the glands of either group. The tissues were obtained at simultaneous autopsies. Preliminary studies on alloxan diabetic animals showed that these rats reacted to thiamine deficiency in a manner similar to normal animals.

**Fibrinolysis in peptone shock.** L. B. JAKUES, M. ROCHA E SILVA (by invitation), A. EVELYN SCROGGIE (by invitation). *Dept. of Physiology, Univ. of Saskatchewan, Saskatoon.* The liberation of histamine and heparin from the liver by peptone, responsible for the symptoms of peptone shock in the dog, has been obtained from the isolated liver using whole blood preserved in silicone for the perfusion fluid (Rocha e Silva, Scroggie, Fidler and Jaques, *Proc. Soc. Exp. Biol. and Med.*, in press). On the addition of peptone, a marked fall in the platelet count of the blood passing through the liver was observed. Liver smears were made and it was found that the agglutinated platelets were filtered out in the liver. Using the "fibrinolytic protamine test" (*Proc. Soc. Exp. Biol. and Med.* 61, 376, 1946), fibrinolysis was observed in the perfusate, accompanying the fall in platelet count.

Fibrinolysis in peptone shock has also been studied using the crystalline soybean tryptic inhibitor of Kunitz. Crystalline soybean inhibitor inhibited fibrinolysis of dog blood produced by peptone in the anterior animal and also the fibrinolytic action of chloroform treated dog serum. It also inhibited the liberation of histamine from rabbit blood cells [*Supported by Fellowships of the Instituto Canada, Brazil and the National Council of Jewish Women of Canada*].

**Excitability of cortical afferent systems in relation to anesthesia.** LEONARD W. JARCHO<sup>1</sup> (introduced by Philip Bard). *Dept. of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore 6, Md.* Paired electrical impulses were delivered to the radial nerve in a series of cats and the resultant potentials recorded from appropriate cortical areas. The interval between stimuli was then plotted against the height of the second response. The resulting excitability curve was found to vary markedly at different levels of anesthesia (pentobarbital sodium).

(1) The deeper the anesthesia, the less the fluctuation in the amplitude of response. This change

is correlated with a decrease in spontaneous cortical activity, which normally interferes with the evoked response by occupation of a portion of the neurones involved. The tendency of the absolute amplitude of response to rise at deeper anesthetic levels is a corroborating observation.

(2) The absolutely unresponsive time of the system increases with deepening anesthesia and may attain four or five times the control duration. When the response is diphasic, the negative deflection always has a longer unresponsive time than the initial positive phase. This suggests a cumulation of anesthetic effect at the further end of the pathway traversed with greater depression at the cortex than in the thalamus.

(3) Under light anesthesia thalamic after-discharge is a prominent feature and its presence causes oscillation in the excitability curve. With deepening anesthesia the after-discharge tends to disappear, and the curve reaches a smooth plateau. Similar changes occur in other afferent systems and have also been observed in the monkey.

The relation of these findings to the behavior of evoked responses during cortical mapping experiments is discussed.

**Integration and disintegration of motor units, unipolar electromyography in neuro-muscular diseases.** HERBERT H. JASPER. *Dept. of Neurology and Neurosurgery, McGill Univ. and the Montreal Neurological Inst. (with the aid of the National Research Council of Canada).* The electrical activity of human muscles, denervated and reinnervated by regeneration after peripheral nerve injuries was compared with that obtained from patients during various stages of paralysis following poliomyelitis, amyotrophic lateral sclerosis and progressive muscular atrophy, neuritis, myasthenia gravis and in muscles affected by traumatic lesions of the spinal cord. Relatively undistorted cathode ray oscilloscope records of action potentials from single motor units and single muscle fibers was obtained by the use of a finely pointed single needle electrode, insulated excepting the point, with a reference electrode on the skin adjacent to the site of the needle insertion. Single motor units in normal muscles appeared as triphasic spikes, usually of smooth contour excepting in the muscles of the face. Highly disintegrated polyphasic motor units were observed (a) during reinnervation with regeneration of an injured nerve supply, (b) during the active degenerative phase of amyotrophic lateral sclerosis and progressive muscular atrophy, (c) during spontaneous fasciculation of muscles, (d) during certain stages of poliomyelitis, and (e) during both the acute and recovery phases of polyneuritis. Spontaneous fasciculations electrographically recorded, were not affected by nerve block, were exaggerated with prostigmine, and were arrested by curare. This

<sup>1</sup> Henry Strong Demson Fellow for 1946-47



was also true for spontaneous fibrillation which was recording from completely denervated muscles as a result of peripheral nerve lesions, in some of the muscles permanently paralyzed by poliomyelitis, and other conditions associated with degeneration of the lower motor neurone. Fibrillation was never observed in muscles paralyzed by upper motor neurone lesions and in certain muscles in complete flaccid paralysis following poliomyelitis, the latter being electrically silent.

**Environment and caloric requirements**  
ROBERT E. JOHNSON and R. M. KARK (by invitation) *U S Army Medical Nutrition Lab, 1849 West Pershing Road, Chicago, Illinois*. It has been widely supposed without good evidence that caloric requirements increase as the environmental temperature decreases. Analysis of information obtained from observers' reports, surveys and ration trials conducted between 1941 and 1946 in various parts of the world provides information on this point.

Reliable data are available on the average day's food which soldiers chose to eat from the rations provided in the desert, the moist tropics, temperate areas, the mountains, and subarctic and Arctic areas. The groups of fifty or more men for whom values are shown were healthy and fit, engaged in moderately hard to hard muscular work of the same general types, and received an abundant supply of acceptable foods so that they could have eaten more had they wished. The data show a straight line correlation between increase in voluntary caloric intake and decrease in mean environmental temperature. In other words, the colder it becomes the more men want to eat. Extremes were 3100 Calories per man per day in the desert at a mean of 93°F and 5000 Calories per man per day in the Arctic at a mean of 20°F. This large difference in voluntary intake cannot be explained by changes in basal metabolic rate, but may be related to the necessity for increased voluntary activity in the cold to maintain body warmth and the work entailed in moving about in cumbersome heavy clothing.

**Subjective responses to small reductions in barometric pressure in subjects with functional joint pathology**<sup>1</sup> H. L. JONES and A. A. SCHILLER (introduced by C. I. Reed) *U S Naval Hospital and Naval Medical Research Inst, Bethesda, Maryland*. Reductions in ambient pressures under 8,000 feet have been considered to be without manifest effect in the normal human subject. Atmospheric pressure variations occurring in "surface weather" have been implicated in altering local pain perception in several disease states.

Pain is said to be augmented most frequently by diminished pressure. However, the validity of this empirical concept has not received experimental challenge, nor has the mechanism for this relationship been adequately explained.

Experiments on the effect of barometric pressures between sea level and 9,000 feet on local pain responses were performed. Five young adults exhibiting symptomatic arthritis or fibrositis (without demonstrable joint or tissue pathology) were selected as subjects because of their potential increased susceptibility to small changes in barometric pressure. Joint pain was graded according to severity. Each subject, unaware of the altitude, served as his own control in that the chamber runs consisted of random order exposures for periods of 20 minutes each at sea level, 3,000, 6,000 and 9,000 feet. Over a three month period 576 pain evaluations were made during a total of 144 twenty minute exposures.

Statistical analysis of the data revealed that although it was not possible to quantitate the degree of joint pain with altitude changes, there was a correlation between altitude exposure and incidence of pain in joints that had been asymptomatic at sea level.

Explanation of the mechanism of this effect must evaluate local factors of anoxia, vascular changes and cellular metabolism.

**Observations on the chemistry of synovial fluid in human subjects** N. R. JOSEPH (by invitation), HARVEY HORWITZ (by invitation) and C. I. REED *Dept of Physiology and of Medicine, Univ of Illinois, Chicago Colleges*. A group of rheumatoid and hypertrophic arthritis patients was observed over a period of nine months with special attention directed toward the physicochemical properties of synovial fluid from the affected joints. In addition to the pH observed *in vivo* with a glass electrode and a needle reference electrode, the following determinations were made pH *in vitro*, total base and chloride, base bound to colloid, electrodialysis, joint fluid volume, and corresponding observations on normal fluids obtained at autopsy in cases with no indications of pathological conditions in the joints. Significant changes in fluid volume, base bound to colloid, total protein and electrodialysis point were observed in the pathological fluids, the values of all these variables being higher than in the normal fluids. High positive statistical correlations among these four variables were noted, with lower or only slightly significant correlations being found among the other variables. For example, there was a high positive correlation between volume and base bound to colloid, but low correlation between both these variables and the pH. Those variables which are strongly correlated with each other appear to be functions primarily of the

<sup>1</sup> The opinions or conclusions contained in this report are those of the authors and are not to be taken as necessarily reflecting the views of the Navy Department.

colloidal composition of the synovial fluid, the others appear to depend also on systemic factors and metabolic activity

The relation of a measurement of enthusiasm-staleness to measurements of physical fitness, for medical students under the accelerated program FREDERIC T JUNG and LILLIAN E CISLER (by invitation) *Northwestern Univ Medical School* The use of an *enthusiasm staleness* questionnaire made it possible to assign to a series of students a score, the *ESS*, which indicated for each student his place on an attitude scale at the time of the test Two different forms of the questionnaire were used, C and D When they were administered on the same day, high correlations were obtained, when one week of routine work intervened, the correlation was  $+0.60$ , when thirty-nine days intervened, including a vacation, the correlation sank to  $+0.13$

No significant drift in the *ESS* was found for the two years that elapsed between first and second applications of the questionnaire to medical students under the accelerated program A significant change for the better was found for an interval which included a vacation

While the vacation was followed also by a rise in the *cardiac recovery index* of the students, it was demonstrated that this rise in *CRI* was not particularly likely to occur in those students who showed the improvement in *ESS*

The *ESS*, which was designed to measure primarily an attitude or mental state, was not found to be correlated significantly with any of the measurements of fitness or physical state

Blood vitamins A, C and E and seminal fluid vitamin C in human male sterility EDWIN C JUNGCK (by invitation), W O MADDOCK (by invitation), J T VAN BRUGGEN (by invitation) and CARL G HELLER *Dept of Physiology, Biochemistry and Medicine, Univ of Oregon Medical School, Portland, Oregon* Instances of male sterility in which no correctable hormonal defects were encountered were subjected to whole blood vitamin C, plasma A and E and seminal fluid vitamin C analyses All subjects exhibited normal vitamin E levels, and occasional subjects exhibited low plasma vitamin A and low whole blood vitamin C levels

Normal seminal fluid was found to contain 10-15 times as much ascorbic acid as is contained in whole blood The majority of the sterility cases exhibited lowered seminal fluid vitamin C levels, no correlations in levels of blood A and C and seminal fluid C could be made

Effects of atropine and estrogens on endometrial blood vessels in intraocular transplants IRWIN H KAISER (introduced by S R M Reynolds) *Carnegie Institution of Washington, Dept of Embryology, Baltimore 5, Md* Atropine halts

rhythmical vascular activity of the endometrium in transplants to the anterior chamber of the rabbit's eye The drug, given intravenously in doses from 0.6 to 6.0 mgm to isolated intact animals, stops constriction of the arterioles without marked change in their tone or increase in the number of functioning capillaries as indicated by the overall color of the graft This is in contrast to the action of adrenalin which interrupts the rhythm by producing vasoconstriction Atropine has no regular effect on the myometrium in these grafts Estrogens, including stilbestrol, also halt the rhythmical activity, requiring from 45 to 60 minutes for maximum effect, the vessels dilate and the number of functioning capillaries increases as indicated by a deeper overall red color in the graft Stilbestrol has been shown not to increase the acetyl choline content of the uterus in the same time period Atropine does not prevent the action of estrogens on endometrial vessels nor does it reverse this action once it is established There are no regular changes in the frequency or duration of myometrial contractions in the grafts after administration of estrogens

These observations necessitate a revision of the so called cholinergic concept of the acute effect of estrogens on the endometrial vessels The increase in acetyl choline content of the whole rabbit uterus observed following estrogen administration is probably due to changes in the myometrium A different mechanism must be invoked to account for the phenomena seen in the endometrium

Modification by anti-histaminic agents of estrogenic effects on endometrial blood vessels in intraocular transplants IRWIN H KAISER (introduced by S R M Reynolds) *Carnegie Institution of Washington, Dept of Embryology, Baltimore 5, Md* Estrogens and histamine produce vasodilatation of the endometrium of the rat The possibility that estrogens act on endometrial blood vessels by local production of histamine or a histamine like substance can be explored by the use of anti histaminic agents One of these, pyribenzamine, causes no change in the color of a transplant of endometrium in the anterior chamber of the eye of an isolated rabbit with intact ovaries The pyribenzamine is introduced in aqueous solution into the conjunctival space It does produce an increase in the frequency and duration of contraction of the myometrium in the graft If a deepening of color due to vasodilatation and increase in the number of functioning capillaries is first produced by administration of estrogen, then pyribenzamine causes a slight decrease in color This, however, may be due to a masking out action of the increased myometrial activity Further studies with other preparations and other anti-histaminics are required to clarify this point

**The effect of hypertension on the blood pressure responses to epinephrine and pentobarbital** L N KATZ, M WILBURNE (by invitation) and S ROBBARD *From the Cardiovascular Dept, Research Institute, Michael Reese Hospital, Chicago, Illinois* The blood pressure responses to intravenous injection of epinephrine (1 mg) in the unanesthetized dog and of anesthetic doses of pentobarbital sodium followed by epinephrine were recorded with the Hamilton manometer, to determine whether a quantitative difference in response could be obtained between normotensive and hypertensive animals

In the unanesthetized animal, epinephrine caused a prompt increase in blood pressure in all animals. After dissipation of the pressor effect, the pressure returned to control levels in the hypertensive dogs, and to slightly lower than control levels in the normal dog.

Intravenous injection of pentobarbital caused a fall of about 40/40 mm Hg in the normotensive dog, in the hypertensive dog the fall in blood pressure was about 40/10.

After about 10 minutes, a second injection of epinephrine was given to the animals anesthetized with phenobarbital. After dissipation of the pressor response, the blood pressure then fell far below control levels in the normotensive animals and these low values persisted for 5 to 15 minutes. However, no such depressor phase was seen in the hypertensive dogs.

**Urine extracts of hypophysectomized dogs administered in different periods of a double histamine experiment** J KAULBERSZ, T L PATTERSON, D J SANDWEISS and H C SALTZSTEIN (by invitation) *Wayne Univ College of Medicine and Harper Hospital, Detroit, Mich* In a new series of dogs the transtemporal method was substituted for the transbuccal employed in our previous studies for the removal of the pituitary gland. Urine extracts were prepared and their influence tested in double histamine experiments on gastric secretion on Heidenhain pouch and fistula dogs.

When the extracts were administered in the first period in all but one of 15 experiments an increase of 12-790 per cent of the total output of free HCl in milliequivalents was noted as compared to the controls. Injection of the extract in the second period did not give any definite change, the difference in the averages not exceeding  $\pm 10$  per cent.

In order to explain this discrepancy double histamine experiments without any extract application was made on the same series of dogs. Although the averages in milliequivalents of 28 experiments did not vary over  $\pm 10$  per cent, nevertheless a decrease resulted in the second period as compared to the first, also the number of experi-

ments in which the secretion was smaller in the second period prevailed (39 per cent as to 29 per cent).

This tendency of the stomach of our dogs to secrete less after the second injection than after the first may be partly responsible for the different results mentioned above. Possibly, another contributing factor is a decreased susceptibility of the stomach cells to the extract for several hours after a period of abundant secretion.

**Inhibition in the auditory nerve** PETER KELLAWAY (by invitation) and H E HOFF *From the Dept of Physiology, McGill Univ, Montreal* When auditory nerve fibers are tetanized by applying to the ear a high intensity tone of 500-1000 cps and the effect of this rapid firing tested by abruptly replacing the tonal stimulus with a slow series of discrete stimuli in the form of clicks, the first click response is greatly reduced in size and each succeeding response only slightly larger than its predecessor so that normal amplitudes are not reached until after about 2 seconds. Cochlear microphonic potentials do not show a similar effect. Yohimbine and other substances which prolong the subnormal period do not increase the phenomenon when injected or when perfused through the perilymphatic channels. Another observation indicates that the phenomenon is not a manifestation of "subnormality". When a low tone is immediately preceded by a high tone the first few nerve responses evoked by the former are diminished in the same way as are clicks, but Galambos and Davis' data on single auditory fibers show that the high tone could not be tetanizing the low tone fibers at a faster rate than the low tone itself because a given fiber responds most rapidly to a tone of its own specific frequency. Thus a 100 cycle fiber will produce more impulses when stimulated by a 100 cycle tone than by a 1000 cycle tone of similar intensity, and accordingly would be subject to greater subnormality when thus stimulated. In fact, the 100 cycle tone produces little or no reduction in subsequent responses.

**Descending nerve fibers subserving heat maintenance functions coursing with the cerebrospinal tracts through the pons** A D KELLER, *Dept of Physiology and Pharmacology, Baylor Univ College of Medicine, Houston, Texas* The observations reported below were confined to acute preparations, i.e., the assay of the heat maintenance powers was carried out the day following the operation.

The brainstem substance which lies directly dorsal to the pons proper (above the transverse pontine fibers and pontine nuclei through which the cerebrospinal bundles descend) can be routinely completely transected without strikingly affecting the animal's heat maintenance powers.

Accordingly, some heat maintenance fibers must descend through the substance of the pons in close relationship with, and probably as a component part of, the cerebrospinal bundles.

At the extreme caudal extent of the pons the entire brainstem substance except the pyramidal bundles, as they become exteriorized on the ventral surface of the trapezoid body, can be routinely transected without eliminating heat maintenance powers. Accordingly, at this level (upper medulla), some heat maintenance fibers definitely course caudally as a component part of the cerebrospinal bundles [*Aided by a grant from the John and Mary R Markle Foundation*].

Failure of sexual development following lesions in environs of the pineal in "senior" female pups. A. D. KELLER, *Dept of Physiology and Pharmacology, Baylor Univ. College of Medicine, Houston, Texas*. Slightly more than a hemisection of the brainstem was executed at the level of the pineal gland, resulting in the destruction of the body of the pineal as well as its ventral prolongations into the brain tissue. Animals were maintained for six months. It was noted in the animals which were sexually immature at the time of operation ("senior" pups) that at autopsy the genital tracts remained infantile. Normally the genital tracts would have become fully developed and the animal would have passed through its first estrus period at some time during this six-month interval.

The question arose as to whether we were dealing with a permanent sex-development deficit or merely with a delay in the onset of sexual maturity—a missing of the first estrus period—of the nature which in our experience frequently occurs following surgery in the environs of the hypophysis in "senior" female pups. This question is being elucidated by maintaining such preparations through several six-month intervals (estrus intervals) after operation and also by restricting the lesion to the dorsal aspects of the brainstem—immediate environs of the pineal—so as to avoid the remote possibility that a temporary hypophyseal disturbance might be the causative factor. We now have an animal in this series prepared fifteen months ago which is as yet sexually infantile.

These observations are entirely compatible with the long standing hypothesis that the pineal elaborates a principle which is essential for the onset of sexual maturity [*Aided by a grant from the John and Mary R Markle Foundation*].

Retention of normal insulin tolerance and adrenal cortex following extirpation of hypophyseal stalk in dog. A. D. KELLER and C. G. BRECKENRIDGE (by invitation), *Dept of Physiology and Pharmacology, Baylor Univ. College of Medicine, Houston, Texas*. The tissue of the hypo-

physeal stalk which is removed in executing a near-total hypophysectomy was removed with a sparing of a sizable amount of the distal pars anterior tissue (stalk removal procedure). The dogs were maintained for from six to twenty-five months after operation. The status of carbohydrate reserves was determined by insulin tolerance tests. Adrenal cortical function was tested by subjecting the animals to an environmental stress of 5°C for an eight hour period, and to the surgical stress of total pancreatectomy. The overall size of the adrenal and the thickness of the adrenal cortex was noted at necropsy.

Most of the dogs showed no noteworthy deviation from the normal in (1) the size of or the function of the adrenal cortex, and (2) the ability to tolerate  $\frac{1}{2}$  or 1 unit of insulin per kilogram of body weight administered subcutaneously. Some atrophy in the adrenal cortex was suspected and a decrease in insulin tolerance was definite in a few of the animals, but in no instance did these deficits approach in magnitude those which are routinely encountered in the near total hypophysectomized dog.

On the basis of these results coupled with those previously published (Arch. Path. 40: 289-308, 1945), it is concluded that the hypophyseal control over the adrenal cortex and over all carbohydrate reserves is mediated by elements located in the cellular population of both the pars tuberalis and pars anterior [*Aided by a grant from the John and Mary R Markle Foundation*].

Studies on blood flow and the efficacy of deep tissue thermogenic agents. C. R. KEMP (by invitation), W. D. PAUL (by invitation) and H. M. HINES, *Depts of Physiology and Physical Medicine, State Univ. of Iowa, Iowa City*. Studies were made on dogs under nembutal anesthesia. Unilateral or bilateral measurements of blood flow through the femoral arteries were made by a bubble flow meter. Tissue temperatures were measured by means of a thermocouple which was housed in a hypodermic needle. Changes in tissue temperatures were induced by application of hot and cold packs, diathermy and infrared lamps.

The studies showed that the external application of heat and diathermy treatments applied to the hind limbs of dogs in doses which were tolerated with comfort by the human were most frequently accompanied by a reduced blood flow with comfort by the human were most frequently accompanied by a reduced blood flow through the femoral artery. In general, the effect was proportional to the degree of temperature rise in the muscle and was more pronounced on the treated limb than on its untreated contralateral control. This effect on blood flow was abolished or lessened by denervation of the limb. No consistent effects of diathermy treatments upon blood flow were

found in experiments where the temperature of the muscle remained unchanged. An elevation of general body temperature by means of diathermy applied to the chest was accompanied by a reduced femoral blood flow. The above changes occurred independently to changes in arterial blood pressure as measured by the Hamilton optical manometer.

Denervation was followed by an immediate increase in femoral blood flow. This increase gradually subsided and returned to approximately normal values within several days. Thereafter a reduced blood flow was observed and at these times diathermy caused a greater elevation in the temperatures of denervated muscles than in non-denervated control muscles.

**Nitrous oxide method for measurement of human cerebral blood flow.** Experimental evaluation of fundamental assumptions. SEYMOUR S KETY (by invitation), MEREL H HARMEL (by invitation), HENRY A SHENKIN (by invitation), and CARL F SCHMIDT, *Dept of Pharmacology, Univ of Pennsylvania, Philadelphia*. The measurement of cerebral blood flow by means of arterial and internal jugular nitrous oxide concentration curves depends for its validity as pointed out in its original presentation (Am J Physiol 143:53, 1945) on the extent to which blood from one internal jugular vein is representative of mixed cerebral venous blood, on the completeness of equilibration of nitrous oxide between brain and blood in a reasonable length of time, and, with respect to absolute values, on accurate evaluation of the partition coefficient of nitrous oxide between brain and blood. Further evidence has been acquired pertaining to these tenets. In a series of simultaneous cerebral blood flow determinations on both internal jugular bulbs in 10 patients (including 2 with unilateral cerebral hemangiomas) the greatest variation between either side and the mean in any one pair was  $\pm 10\%$ , the average variation was 5%. Information on the extent to which internal jugular bulb blood is contaminated by blood from extracerebral sources has been obtained by injecting the dye T 1824 into the external carotid artery (exposed in the course of cerebral arteriography) and measurement of the resultant concentrations of dye in external and internal jugular blood. Results to date indicate a negligible amount of contamination of internal jugular blood with extracerebral blood. Techniques were developed for determination of the partition coefficient of  $N_2O$  between brain and blood in vivo and in vitro. Results of these studies indicate practically complete tension equilibrium of  $N_2O$  between brain and cerebral venous blood within 10 minutes and a partition coefficient ( $N_2O$  per gm of brain -  $N_2O$  per cc of blood) of 1.0 instead of our previous tentatively accepted value of 1.3.

**Total body fluid, fat and active tissue in starvation and subsequent rehabilitation.** <sup>1</sup>ANCEL KEYS, JOSEF BROZEK (by invitation), OLAF MICKELSEN, AUSTIN HENSCHEL and HENRY LONG-STREET TAYLOR, *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis*. Thirty-two "normal" young men who lost 24 per cent of their body weight in 24 weeks of semi starvation were studied at the start (C) and end (S24) of their weight loss and after 12, 20, 34 and 58 weeks of rehabilitation (R12, R20, R35 and R58, respectively). X-ray studies indicated no change in bone minerals. Extracellular fluid (thiocyanate) showed only minor absolute changes at any time (average maximum +4 and -3%). There was considerable relative edema (+44% relative thiocyanate space) at S24, disappearing at about R20 when control body weight was regained. Clinical edema was only barely recognizable when about 9% of the body weight comprised excess fluid, grade 2+ edema being associated with about 12% excess fluid. Per kg of body weight, plasma volume and extravascular thiocyanate space were strongly correlated ( $r = +0.706$ ) in 85 pairs of observations ranging from the normal nutritional state to the condition at S24. Total body fat was estimated densitometrically with correction to normal hydration and bone mineral proportions. Mean total kg of body fat was 9.66 at C, 2.74 at S24, 5.88 at R12, 13.41 at R20, 14.30 at R34, 10.61 at R58. Estimated "active tissue" weight (body weight less sum of fat, bone mineral and thiocyanate space) declined 27% in semi-starvation and was slowly restored, reaching the control level between R33 and R58, that is 9 to 12 months after the end of semi starvation.

**Effect of gonadotropin on the function of adrenal cortical tumors in ovariectomized, restricted  $C_3H$  mice.** JOSEPH T KING, M B VISSCHER and CARMEN B CASAS (by invitation), *Dept of Physiology, Medical School, Univ of Minnesota*. Evidence has already been presented to indicate that the anestrus observed in the underfed rodent is due to pituitary inhibition.

The constant subestrus associated with adrenal cortical adenomata seen in the castrate female  $C_3H$  mouse when fed ad libitum does not appear when dietary calories are restricted to 66% of the normal intake while the diet contains the same amounts of protein, vitamins, and minerals as ingested by the controls. The calorie-restricted animals show the same type of adrenal cortical tumors seen in full-fed animals.

It is evident that the full-fed castrate mouse has developed an endogenous source of estrogen. Since the restricted mouse has the same adrenal tumor and since it is possible that the adrenal

<sup>1</sup> Sponsorship for this work will be acknowledged in final publication.

is the source of the estrogen in the full-fed mouse it became important to determine whether the estrogen-producing tissue is responsive to gonadotropin as has been shown by others to be true of the ovary of the underfed rodent

Assayed commercial gonadotropin was injected into restricted, ovariectomized mice when the adrenal tumors were well developed. The largest dose given was 10 Cartland Nelson units daily for 8 days. There was no evidence of estrogenic stimulation in the vaginal smear.

It is apparent that the estrogen-producing tissue, whether in the adrenal or elsewhere, is either not responsive to gonadotropin or is much less so than ovarian tissue.

**Diurnal cycle in activity and body temperature of rabbits.** NATHANIEL KLEITMAN and THEODORE ENGELMANN (by invitation) *Dept of Physiology, Univ of Chicago*. With continuous access to food, the activity of rabbits, as measured by actograms and by recorded activation of a self-starting electric clock, was lowest during the day time hours, with a minimum about noon, and highest during the night. Their rectal temperature, as determined by a clinical thermometer, was also low during the day, but tended to rise during the evening. When food was available only from 9-10 A.M. to 3-4 P.M., the animals quickly adapted themselves to this routine, but did not eat as much as when access to food was uninterrupted. Activity became more decidedly monophasic, increasing sharply in the morning, prior to the time of feeding, and continuing at a high level during the day. The rectal temperature showed a marked rise during the feeding period, reaching its high level in the afternoon, instead of late in the evening.

By the electric clock records of the actual time spent in activity, it was found that the rabbits were active on the average, from 3-4 to as many as 20-25 minutes per hour, as a diurnal range, and adding up to a total of 5-6 hours of moving about out of every 24.

Although usually considered polyphasic, rabbits, under ordinary laboratory conditions, show a distinct 24 hour cycle of activity and body temperature. The tendency to a night time high, when access to food is continuous, can easily be modified by making food available for only a few hours during the day.

**The effect of hemorrhage on the plasma amino nitrogen of the diabetic dog.** DANIEL L. KLINE (introduced by Magnus I. Gregersen) *Dept of Physiology, College of Physicians and Surgeons, Columbia Univ*. The control arterial plasma amino N levels (estimated by the manometric ninhydrin method) in dogs made diabetic by the injection of alloxan or by pancreatectomy, were somewhat above the previously reported

normal range (Am J Physiol 146 654, 1946), being higher in the depancreatized animals. The prehemorrhage femoral arterio venous amino N differences were also elevated in the diabetic animals, especially in the depancreatized dogs. This indicates greater liberation of amino N from the legs in diabetic, as compared with normal dogs.

The animals were bled out and 25 per cent of the bleeding volume was immediately replaced. No significant difference was found between the bleeding volumes or the survival times of insulin deficient and of normal animals. After bleeding, the femoral arterio venous amino N differences in the diabetic dogs were higher than those observed in untreated, similarly hemorrhaged animals. However, when one compares the rise above their initial values, the arterio venous curves of the alloxan-treated dogs closely resembled those of the normal series, whereas the curves of the depancreatized animals are much higher. During the first hour after bleeding, there was a far greater outpouring of amino N from the legs of the pancreatectomized dogs than was observed in the other two series. The arterial plasma amino N levels rose approximately the same amount in the alloxan treated and untreated hemorrhaged dogs, but the rise was considerably less in the depancreatized, bled animals. This occurred in spite of the much greater liberation of amino N from the legs of the pancreatectomized preparations.

**Effects of severe anoxia and their amelioration.** R. F. KLINE *Univ of Virginia*. In a series of exposures to severe anoxia it was found that all animals (cats) showed development of critical conditions, usually within two or three minutes, between the 30,000 and 40,000 ft alt equiv level. Arterial pressure and heart rate fell simultaneously, and the respiratory rate, previously elevated by the exposure, also showed a sharp decrease. Reduction of barometric pressure was made to about the 40,000 ft level in 4 min. Death was prevented by a rapid restoration, i.e. within about 30 secs, of sea level conditions.

Administration of oxygen in high concentration in the (continuously-ventilated) chamber afforded protection in such experiments. CO/O<sub>2</sub> in the ratio 13/87 was equally or more useful, this gas mixture maintained arterial pressure and cardiac and respiratory rates at normal levels up to the 40,000 ft alt equiv level. Maintenance of animals was possible at this altitude with CO/O<sub>2</sub> for a period of 1 to 3 min. In the concentration 25/75, good results were obtained even at 43,000 ft for significant periods.

The CO/O<sub>2</sub> mixture was also strikingly effective in restoring animals after severe circulatory and respiratory depression had been produced by exposure at 33,000 ft alt equiv for 5-15 mins. Arterial pressure, heart and respiratory rates were

restored rapidly, i.e. within a minute or so, under this treatment  $\text{CO}_2/\text{O}_2$  was superior to oxygen alone in restoring respiration to normal [*Work carried out under a contract between U S Navy, Office of Naval Research, and the University of Virginia*]

The round window membrane of the cochlea H G KOBRAK (introduced by Lester R Dragstedt) *Division of Otolaryngology, Dept of Surgery, The Univ of Chicago* The function of the inner ear cannot be understood satisfactorily unless detailed information on the physical characteristics of various inner ear structures becomes available. A study of the literature reveals that the round window membrane (Fenestra cochleae secundaria) has not been studied extensively in the past.

An anatomical and histological study preceded the physical tests. Serial sections of the round window membrane were made (Human temporal bone). A study was made of the anatomical basis of physical properties (Homogeneity of the membrane, boundary conditions, thickness, size of surface area, arrangement of elastic fibers etc.). The weight of the round window membrane was determined and the density of the membrane calculated.

Functional tests were taken on the isolated round window membrane and on the round window membrane in situ. The excursions of the membrane due to static or acoustic pressure changes were recorded optically (moving picture films and recording by mirror). The volume-elasticity was studied experimentally. The phase difference between stapes and round window membrane was observed by simultaneous exposure of the two cochlear windows. The amplitude of the movements of the round window membrane was found to be larger than, and opposite in phase to, the stapes movements. The sound shadow theory of the round window is discussed. The round window membrane when properly observed can be used as a dynamic manometer of the cochlea. The acoustic vibrations of the human round window membrane (fresh cadaver specimen) in response to music are demonstrated in a moving picture film.

The protein anabolic property of testosterone propionate in normal, castrated, adrenalectomized and hypophysectomized rats CHARLES D KOCHAKIAN, JEAN G MOE (by invitation), M LUCILE HUNTER (by invitation) and CONSTANCE E STETTNER (by invitation), *Dept of Physiology and Vital Economics, School of Medicine and Dentistry, Univ of Rochester, Rochester, New York* The injection of testosterone propionate into adult male rats on a constant food intake produces a decrease in urinary nitrogen excretion accompanied by an increase in body weight. If the injections are continued after attainment of maximum effects, there is a gradual return of

the nitrogen excretion and the body weight to the pre-injection level. On cessation of injections there is a decrease in body weight and an increase in urinary nitrogen excretion for several days.

The testosterone propionate produces the greatest effects in the castrated rat, somewhat lower effects in the normal rat and the adrenalectomized-castrated rat maintained with injections of desoxygenocorticosterone acetate and in the hypophysectomized rat only about one third those obtained in the castrated rat. Therefore, although the protein-anabolic effect of testosterone propionate is not mediated through either the adrenal glands or the pituitary, the upset in the metabolic status produced by the removal of either of these glands, especially the pituitary, modified the "N-hormone" property of this steroid ester.

Excretion of neutral red by the liver and kidneys S A KOMAROV, RICHARD KOLM (by invitation) and HARRY SHAY *Fels Research Institute, Temple Univ School of Medicine* Experiments were performed under nembutal anesthesia on dogs and cats with a urinary bladder fistula, cannulated common bile duct and ligated cystic duct. Solutions of neutral red in saline were injected into the external jugular vein, in doses of 4.1 to 11.7 mg per kg body weight. Dye excretion in bile and urine was studied for third to seventh hour after injection. The results of these experiments demonstrate that greatest excretion occurred through the liver and not the kidneys. In two hours 39.4 to 46.9% of the injected dye was excreted in the bile and only 3.2 to 7.0% in the urine. In four hours 43.8 to 58.0% of the injected dye was excreted by the liver and 6.5 to 9.9% by the kidneys.

Maximal concentrations in the bile ranged from 210 to 894 mg %. In most of the experiments the dye concentration reached was directly related to the dose. The peak usually appeared in the first hour following injection. Maximal concentrations in the urine were observed during the first hour in 50% of the experiments and were reached in the second hour in the remainder. The concentrations of dye appearing in the urine varied from 8.0 to 33.2 mg %. Because of possible duodenal regurgitation, the high concentration of the dye appearing in bile has an important bearing on the evaluation of the Neutral Red test for gastric secretory function clinically.

Gastric mucin a new quantitative method for its determination Secretion of mucin under various conditions S A KOMAROV, HERMAN SIPLET (by invitation), and HARRY SHAY *Fels Research Institute, Temple Univ School of Medicine* A quantitative method for the determination of mucin in the gastric juice and gastric contents has been developed. This method is based upon the determination of glucuronic acid—



characteristic component of the prosthetic group of mucoproteins—after a preliminary hydrolysis of the material with 3N HCl. The liberated glucuronic acid is determined photoelectric colorimetrically by the Tollens' (Z physiol Chem 61 95, 1909) Naphthoresorcinol reaction as outlined by Maughan, Evelyn, and Browne (J B C 126 567, 1938). With gastric mucin and its derivatives we have found that the resulting product is a two component color system with two maxima of light absorption, at 565 and 400 mμ. Better recoveries were obtained with mucin, mucosin sulfuric and chondroitinsulfuric acids when colorimeter readings using both bands were analyzed according to Knudson, McLoche and Juday (Ind and Eng Chem, Anal Ed 12 715, 1940).

Our method was found to be specific for mucin in the gastric juice, with an accuracy within 10% and good reproducibility. A number of alkaline mucus specimens secreted under various conditions contained mucin in concentrations from 266 to 1342 mg/100 ml. The presence of mucin in solution in highly acid gastric juice, first reported by Babkin has been established by this method. Concentrations of mucin thus far observed in sham feeding ranged from 58 to 248 mg/100 ml and in histamine juice from 3 to 23 mg/100 ml. The higher concentrations were always found at the beginning and towards the end of each secretory period. The greater part of the mucin contained in the alkaline mucus was found to be readily soluble in 0.15 N HCl.

Renal plasma flow and glomerular filtration in the dog in relation to arterial hypertension and renal damage. F. J. KOTTKE and W. G. KUBICEK (introduced by M. B. Visscher) *Dept of Physiology, Univ of Minnesota Medical School, Minneapolis*. Mechanical disturbance of the renal blood supply together with renal artery nerve stimulation with a 2 c.p.s. sinusoidal alternating current 16–20 hours daily resulted in a severe uremia in one dog. Although renal plasma flow glomerular filtration were reduced nearly to zero during periods of stimulation, arterial hypertension did not develop. Later, with an increase of the renal plasma flow and as the uremia diminished, arterial hypertension developed during stimulation. Morphological examination of these kidneys showed evidence of hypertrophy, presumably preceded by atrophy.

In a second animal studied for 21 months 3 successive sets of electrodes were attached to the renal arteries and associated nerves, subdiaphragmatic and supradiaphragmatic splanchnics respectively as each set of electrodes became non-functional. Blood pressure remained elevated only during periods of renal artery nerve stimulation and subdiaphragmatic splanchnic stimulation. Following 40 days of supradiaphragmatic splanchnic

stimulation, (480 days after application of renal artery nerve electrodes) arterial hypertension persisted with or without stimulation over a 4 month period. Postmortem examination revealed completely occluded renal arteries, atrophy of one kidney and hypertrophy of the other. Collateral circulation was the sole source of renal blood supply. Numerous renal clearance tests were performed on this animal and at no time was any abnormality of renal plasma flow or glomerular filtration revealed.

These studies illustrate the occasional inadequacy of renal clearance tests to reveal extensive renal damage and that hypertension does not necessarily develop during severe renal ischemia.

Blood pressure changes in response to electrical and chemical stimulation of the cerebral cortex. WILLIAM F. KREMER (introduced by C. L. Gemmill) *Depts of Pharmacology and Neurosurgery, Univ of Virginia Medical School*. During an investigation of the functional characteristics of cortical blood pressure centers in dogs, the need was felt for a more physiological stimulus than the generally used electrical stimulus. Several chemical compounds (epinephrine, ephedrine, strychnine, prostigmine and acetyl beta methylcholine) were tried for this purpose. Only acetyl beta methylcholine proved to evoke a vasomotor response. Local cortical application of small pieces of blotting paper soaked with a 2.5 per cent solution of this drug produced characteristic blood pressure changes, which, when compared with those obtained by electrical stimulation, showed more detail, were more pronounced and of longer duration. Also, the responsive area could be outlined with greater accuracy. Upon such stimulation of the posterior sigmoid gyrus (motor cortex) and an area in the anterior cingulate gyrus, an abrupt blood pressure drop of 30 to 50 mm Hg was obtained with a latency of 30 to 40 seconds and a duration of 2 to 3 minutes. This fall was further characterized by the appearance of vasomotor waves of the third order. The effect was prolonged by simultaneous application of prostigmine and abolished by pontocaine HCl.

These experiments establish the usefulness of acetyl beta methylcholine as a cortical stimulant and amplify our information of the cortical vasomotor function. They may further support the concept of chemical transmission of stimuli in the central nervous system.

A shielded silver electrode with mercury leads designed for prolonged stimulation experiments. W. G. KUBICEK and F. J. KOTTKE (introduced by M. B. Visscher) *Dept of Physiology, Univ of Minnesota, Minneapolis*. Number 18 fine silver wire is wrapped around a mandrel and soldered to a hollow stainless steel terminal which protrudes out through the side of the mold. The



mandrel has a flat metal projection which forms a slow in the electrode block through which the nerve is admitted. The mandrel is supported at each end by the walls of the mold in a position which provides proper spacial arrangement for the silver wire electrode and the stainless steel terminal. Powdered lucite is then forced into the mold under a pressure of approximately 1000 lbs./in.<sup>2</sup> and a temperature of 170 C. Following return to room temperature the walls of the mold are removed and the mandrel and its flat projection is driven out leaving a lucite block with a slot on one surface and the silver wire electrode imbedded in the lucite surrounding the lumen of the tunnel formerly occupied by the mandrel. The hollow stainless steel terminal is filled with mercury and a mercury filled rubber tube attached. A similar stainless steel terminal is then inserted into the distal end of the rubber tube. An obturator for the slot in the lucite block is molded by obtaining a wax impression from which a plaster cast is formed.

Electrodes and leads as described were attached to the splanchnic nerves of dogs and remained in good condition for as long as six months in one experiment at which time the animal was sacrificed. Rein thermistors with silver leads have been constructed by this technique.

**Reflex activity of the frog's small-nerve motor system** S. W. KUFFLER, Y. LAPORTE and R. E. RANSMEIER (introduced by R. W. Gerard) *Dept of Physiology, The Univ of Chicago*. Small diameter motor nerve fibers have been studied recently in detail, they are widely distributed, set up local contractions around the neuromuscular junctions, and their activity is accompanied by distinct electrical responses (small-nerve junctional potentials, s.j.p.'s) resembling curarized endplate potentials.

On electrical stimulation of the central portion of cut peripheral nerves in decapitated or lightly anaesthetized animals, two types of reflexes are set up in muscles. (1) Small-nerve reflexes, accompanied by slowly rising and well maintained tension. The discharges from the cord in small-nerve fibers give rise to s.j.p.'s, which follow the rate of afferent nerve volleys up to 15-20 per sec. The cord thus responds to afferent nerve stimuli first with small-nerve reflexes. Only with strong afferent nerve stimuli or with submaximal ones exceeding a critical frequency does it set up (2) the well-known twitch reflexes, accompanied by propagated muscle impulses. Small-fiber reflexes appear to be part of normal activity well suited to maintain appreciable tension for prolonged periods. Both types of reflexes may be active simultaneously. Small nerve reflexes are also easily elicited by gentle touch of the frog's skin, while stronger stimuli of any kind set up twitch re-

sponses. This type of reflex excitation, however, cannot be well controlled.

Curarine blocks neuromuscular transmission of the small-nerve system in concentrations which do not affect the twitch response set up by large nerve fibers. A similar selective block is obtained with novocaine application to nerve trunks in concentrations which do not prevent conduction in large motor nerve fibers.

**Venous pressure in the extremities of man during positive acceleration on a centrifuge** E. H. LAMBERT and O. L. SLAUGHTER (by invitation) *Acceleration Lab and Section on Physiology, Mayo Foundation, Rochester, Minnesota*. Measurements of venous pressure in the extremities were made in ten men during 71 exposures to positive acceleration in the Mayo centrifuge. Pressures were recorded by means of a strain gauge manometer which activated a galvanometer. Accelerations were attained in 2 to 3 seconds after 1.5 g was exceeded and were usually maintained for 15 seconds.

Prior to centrifugation pressure in the greater saphenous vein at the ankle averaged 39 mm Hg (vertical distance from ankle to third interspace at the sternum was 51 cm). With the start of the centrifuge pressure was reduced about 15 mm Hg owing to tangential acceleration. However, when positive acceleration exceeded 1.3 g, venous pressure began to rise and at the end of 15 seconds at 2.5, 3.0, 3.5 and 4.0 gram venous pressures were 81, 90, 93 and 99 mm Hg, respectively. Generally, 45 to 60 seconds' exposure to acceleration was required before venous pressure at the ankle reached a plateau and would support a column of blood sufficiently high to return blood to the heart. A somewhat similar circumstance pertained in measurements of venous pressure in the arm.

Since compensatory recovery of arterial pressure and recovery of vision begin after the fifth and tenth seconds of exposure to acceleration, respectively, it is evident that cardiovascular compensation becomes effective despite lack of venous return from at least the more dependent parts of the extremities. This is in harmony with the fact that the amount of blood pooled in the legs during this time is relatively small (see Slaughter and Lambert).

**Arteriolar elasticity: implications of the validity of Poiseuille's law in perfusion with Ringer's solution** H. LAMPORT *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn*. In perfusion of isolated regions with Ringer's solution, Poiseuille's law has been found valid. Flow rate is proportional to perfusion pressure (Pappenheimer and Maes, *Amer J Physiol*, 137: 187, 1942). Conclusions concerning the elasticity of arterioles can then be drawn. They may be so

rigid under pressure changes that discrepancies resulting from their slight distensibility have not yet been observed. Or, each arteriole, although distensible, may stretch in length and in calibre so that the two effects, one tending to decrease flow rate, the other to increase it, offset each other and flow rate remains proportional to pressure as though the arteriole were rigid. Lastly, individual arterioles may act differently, some reducing their hindrance to fluid flow while others increase theirs, as pressure rises, but so that statistically total flow rate remains proportional to perfusion pressure (Howell's Textbook of Physiology, 1946, p 652). The hypothesis that offsetting stretching occurs equally in all arterioles is analyzed so that proper data for its verification can be sought.

When  $V$  is the volume and  $R$  the radius of the lumen of a short length  $L$  of arteriole,

$$\frac{1}{3} dV/V = dR/R = dL/L$$

A consequence of these relationships, after simplifying approximations are made and assuming the volume of vessel wall to be invariant, is an expression relating the circumferential and longitudinal moduli of elasticity of the arteriole wall. The same analysis with different numerical results applies to pulsation caused by the heart beat if, as appears likely, Poiseuille's law for viscous fluids remains applicable.

**Choices of salts and water by normal and hypertensive rats with and without desoxycorticosterone.** E M LANDIS and M ABRAMS (by invitation). *Dept of Physiology, Harvard Medical School, Boston, Massachusetts.* Rats were made hypertensive by bilateral renal decapsulation and application of molded latex sheaths which produced perinephritis and hypertension within 15 to 20 days in 80 per cent or more. Duplicate groups of 3 rats each were arranged to include a total of 6 normals, 6 moderate hypertensives (160 to 180 mm Hg systolic) and 6 severe hypertensives (180 mm Hg systolic and over). The six groups of 3 rats were each given continuous access to 6 drinking bottles containing water, 171 M NaCl, and in successive experiments lasting 12 to 20 days (a)  $\text{NH}_4\text{Cl}$ ,  $\text{CaCl}_2$ ,  $\text{MgCl}_2$ ,  $\text{KCl}$ , (b)  $\text{NaI}$ ,  $\text{NaNO}_3$ ,  $\text{Na}_2\text{SO}_4$ ,  $\text{Na}_2\text{HPO}_4$ , and (c)  $\text{Na}$  citrate,  $\text{NaSCN}$ ,  $\text{NaHCO}_3$ , and  $\text{NaBr}$ . Intakes were recorded by daily weighings of the 6 bottles. Conclusions were based on intakes totalling 30 or more rat days. Blood pressures and body weights were recorded twice weekly. Purina and salt poor diets were used in separate series.

Moderately hypertensive rats showed an aversion to  $\text{NaHCO}_3$  and  $\text{NaCl}$ , they substituted an equal volume of pure water without an increase in total fluid. Neither moderate nor severe hypertensives showed any significant appetite for the ions which are said to affect hypertension, viz  $\text{NH}_4\text{Cl}$  (171 and 043 M),  $\text{MgCl}_2$ ,  $\text{NaSCN}$ ,  $\text{NaNO}_3$ .

Severely hypertensive rats exhibited some sodium aversion and also a significant polyuria. They tended to take more  $\text{NaBr}$ , with resulting drowsiness, anorexia, loss of weight, and transitory lowering of blood pressure. Desoxycorticosterone acetate, 25 mg in oil, was then injected subcutaneously daily into one half these rats, viz 3 normals and 6 hypertensives, the other 9 acting as controls for each group. Choice consisted of water,  $\text{NaCl}$ ,  $\text{NaHCO}_3$ ,  $\text{KCl}$ ,  $\text{NH}_4\text{Cl}$  and  $\text{NaBr}$ . Intakes of  $\text{NaCl}$ ,  $\text{NaHCO}_3$  and total fluids increased markedly in both normal and hypertensive rats.

**Sympathin I-mimetic action of N-alkyl analogues of epinephrine.** A M LANDS, V L NASH (by invitation), H M MCCARTHY (by invitation) and B L DERNINGER (by invitation). *Pharmacological Research Labby Frederick Stearns and Co., Division of Sterling Drug Inc. Detroit, Michigan.* The vasodepressor action demonstrable with epinephrine is intensified by the substitution of larger alkyl groups on the nitrogen. With the primary amine (nor epinephrine) vasodepression is seldom seen, but is distinct with the N-ethyl and is prominent with the N-isopropyl analogues. This last compound (O-4, 1024) is an intravenous dose of 0.6 micrograms/kg in anesthetized dogs causes an average reduction in mean carotid blood pressure of 38 mm Hg lasting 2 to 4 minutes. The intramuscular injection of 0.1 mg/kg caused an average reduction of 48 mm Hg lasting from 44 to more than 207 minutes. Placed directly into the duodenum in doses of 0.5 mgm/kgm pressure is reduced 39 mm Hg for 9 to more than 137 minutes. The above changes in blood pressure are accompanied by marked tachycardia. Similar cardiac effects can be demonstrated with the perfused frog and rabbit hearts. Unanesthetized dogs given 0.1 to 0.5 mg/kg orally, may show a slight rise in systolic pressure during the time of maximum tachycardia but as this effect diminishes systolic pressure falls and may be as much as 30 mm Hg below normal after 60 minutes. Recovery is then gradual.

Other sympathetically innervated organs are inhibited by O-4, 1024 as follows, perfused guinea pig lung 0.01 mgm, isolated guinea pig ileum (Magnus method) 1-50 M (million), isolated rabbit uterus 1-20 M, isolated guinea pig uterus 1-4 M, rabbit ileum and colon in situ 0.10 to 0.25 mg/kg intravenously, estrogen sensitized rabbit uteri in situ 0.10 mg/kg intravenously. Acute toxicity by intraperitoneal injection into albino mice is approximately 460 mg/kg.

The removal of the beta hydroxyl to give 1 (3', 4'-dihydroxyphenyl) 2 iso-propylaminoethane HCl results in a compound wherein the effects described above are either missing or greatly diminished. The alcoholic hydroxyl of epinephrine and its alkyl analogues appears to be important for the smooth muscle relaxation described here.

**Steroid depression in *Rana pipiens*** WILLIAM B. LANGAN (introduced by Charles Haig) *Dept of Physiology, New York Medical College, Flower and Fifth Avenue Hospitals, New York, N. Y.* Experiments are in progress relating to the induction of extraseasonal ovulation in *Rana pipiens* with steroid hormones. The steroid hormones, carried in sesame oil, have been introduced into each of three hundred frogs with a single intra-pleuroperitoneal injection. The hormones injected were (1) progesterone (lutoclylin),<sup>1</sup> (2) alpha-estradiol dipropionate (di-ovoclylin),<sup>1</sup> (3) testosterone propionate (oreton),<sup>2</sup> and (4) desoxycorticosterone acetate (cortate).<sup>2</sup> Frogs were kept at a temperature of 18°C to 20°C. No obvious signs of depression were noted, for quantities of hormones ranging from 0.02 mg. to 1.0 mg. However, symptoms of a depressed state became apparent when 2.0 to 2.5 mg. of progesterone and desoxycorticosterone were injected. The frogs exhibited a slowed response (1) in hopping and righting themselves from a supine position, and (2) rested, relaxed on their abdomens with nose down, finally the frogs showed no attempt to right themselves. This sequence of events occurs within a period of three to five hours after injection and may persist for three to five days. This indicates that sufficient amounts of certain steroid hormones will produce a condition of marked depression in *Rana pipiens*.

Choosing the inhibition of the righting reflex as a criterion of a stage of depression, the above mentioned steroid hormones were tested in quantities ranging from 2.5 mg. to 10.0 mg. on both male and female animals. The results indicate that progesterone and desoxycorticosterone are very effective in producing the depression syndrome whereas estradiol and testosterone are ineffective.

**Concealed auriculo-ventricular conduction, effect of blocked impulses on formation and conduction of subsequent impulses** R. LANGENDORF (introduced by L. N. Katz) *From the Cardiovascular Dept., Research Inst., Michael Reese Hospital, Chicago, Illinois.* An impulse which penetrates into the A-V junction without traversing it, concealed A-V conduction, gives indirect evidence by its influence on the transmission time or on the formation of a subsequent impulse. This mechanism may explain otherwise unexpected complex arrhythmias in man.

Two instances observed in man are reported which demonstrate the effect of concealed A-V conduction. In one with second degree A-V block, some impulses occurring late in diastole are conducted with a P-R longer than that of those occurring earlier in diastole. This occurs whenever

a blocked P precedes the conducted impulse at a time in the cycle just before its conduction to the ventricles can be expected. The disturbance in this patient is analogous to that produced by Lewis and Master in the dog's heart by "shifting the middle (blocked) auricular beat" in 2:1 A-V block, so that the middle P occupies a different position in the cycle with respect to the "phase of interference." A further analogy was found in that concealed A-V conduction not only postponed the transmission of the succeeding impulse but on occasion actually prevented its transmission.

A second instance demonstrates a disturbance of impulse formation due to blocked reciprocal impulses, leading to a complex arrhythmia which could only be understood on the basis of concealed A-V conduction.

**Effects of chemical agents on metabolism and function of synapses and fibers in sympathetic ganglia** M. G. LARRABEE, J. M. POSTERNAK<sup>1</sup> (by invitation), and D. W. BRONK, *Johnson Foundation, Univ. of Pennsylvania.* These experiments concern effects on nerve cell metabolism caused by certain chemical agents in concentrations sufficient to prevent transmission over synapses and fibers in perfused sympathetic ganglia of cats. Metabolism was measured by the rate of fall of oxygen tension within the ganglion when perfusion was stopped, the oxygen tension being determined with a tiny, suitably-polarized platinum electrode thrust into the ganglion. Conduction over B and C fibers passing through the ganglion without synapse, and the response of ganglion cells to synaptic excitation, were also recorded.

Different depressants contrast in their metabolic effects as well as in specificity of action on synapses compared with B and C fibers.

Sodium pentobarbital reduces the resting metabolism even in concentrations which depress but do not completely block synaptic transmission (0.3-0.4 mM). Five or ten times higher concentrations are required to block conduction over B or C fibers than over synapses.

Ethyl alcohol also reduces resting metabolism in concentrations (1 to 5%) which depress ganglionic function, but exhibits no preferential action on synaptic compared with axon conduction.

In contrast with these metabolic effects, cocaine, which blocks synapses in concentrations less than 0.3 mM, does not depress resting metabolism in even 5 times this concentration.

Curare similarly blocks synapses without effect on resting metabolism.

These results indicate that while depression of transmission by some anesthetics may be due to

<sup>1</sup> Lutoclylin and di-ovoclylin were supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

<sup>2</sup> Oretone and cortate were supplied by Schering Corporation, Bloomfield, New Jersey.

<sup>1</sup> Fellow of the Swiss Foundation for Medico-Biological Studies.

depression of metabolism, certain other anesthetics and other chemical agents act through a mechanism not involving a reduction of metabolism.

The effect of the fatigue of static effort upon stance oscillations. ELEANOR M. LARSEN (introduced by Walter J. Meek.) *Dept. of Physiology, Univ. of Wisconsin Medical School, Madison*. The standing position exhibits balance oscillations which may be increased or decreased by various factors. If fatigue is a disrupting factor in balance it might be reflected in a change in the pattern of oscillations.

Stance oscillation data, 68 sets of 25 serial observations, were obtained before and after fatiguing effort of the lower extremities on 9 young women. The magnitude of balance oscillations was increased, decreased, or both, depending upon individual susceptibility to fatigue. The usual mean location of the balance oscillations was consistently disrupted, the amount and direction being variable. Disruption of the mean locus and differences in magnitude indicate physiologic change since oscillation patterns are individual and repeatable. Possible interpretations of the variance in oscillation pattern might be the following: these changes suggest weight redistribution of circulatory origin resulting from blood pooling in the lower extremities, concurrent subacute cerebral hypoxia could release lower equilibratory mechanisms from higher inhibitory control, thus producing hypertonia of antigravity muscles and subsequent decrease in oscillations, fluctuating dominance of higher or lower neural control and an imbalance in the static equilibratory mechanisms might be reflected in an increase in the magnitude of oscillations, and transient changes in magnitude of oscillations and in mean locus might create repetitive volleys of sensory stimuli from tonic anti-gravity muscles which in excess are expressed as a sensation of fatigue. [Aided by a grant from the Wisconsin Alumni Research Foundation.]

The effect of the fatigue of static effort and of continued standing upon the point of balance in recumbency. ELEANOR M. LARSEN (introduced by Walter J. Meek.) *Dept. of Physiology, Univ. of Wisconsin Medical School, Madison*. Investigators have reported a blood shift to the vascular reservoirs of the muscles of the lower extremities following activity.

The recumbent height and balance point of 17 young women were determined on a balance table. Static effort fatiguing the lower extremities was performed followed by brief standing and immediate redetermination of recumbent height and balance point. The recumbent height and balance point of 12 young women were also determined before and after continued standing.

Static effort induced transient lowering of the balance point in 18 of the trials, with no effect in 3

The lowering ranged from 0.00 to 0.90 centimeter. Continued standing resulted in lowering in 16 trials, with no effect on 1 individual. Amounts varied from 0.00 to 0.70 centimeter. The effect of the static effort was slightly greater than that produced by continued standing, however, both resulted in transient lowering of the balance point in a significant proportion of cases. The shift in weight balance, although the individual deviations were statistically insignificant, may represent considerable pooling of blood in the lower extremities which might result in decreased circulation to the head and subsequent hypoxia in higher neural centers. Changes in the height of the weight center stimulate equilibratory mechanisms. It is therefore suggested that the weight redistribution, the accompanying stimulation of equilibratory mechanisms, and the hypoxia of neural centers may constitute primary factors in creating the complex sensation of fatigue.

The mixing of dye and of red cells in the cardiovascular system. HAMDEN C. LAWSON and DAVID T. OVERBEY (by invitation) *Dept. of Physiology, Univ. of Louisville School of Medicine*. Evans Blue dye, T 1824, was added to heavy suspensions of red blood cells freshly prepared by centrifuging heparinized dog's blood, and the mixture was injected intravenously into barbiturized dogs. The cell plasma ratio and the plasma dye concentration of circulating blood were determined on arterial samples drawn at one-minute intervals thereafter. Although later portions of the dye disappearance curve (between 10 and 20 minutes) fit a straight line if the logarithm of dye concentration is plotted against time, concentrations for the first 3 to 10 minutes always lie above this line. Fairly good fits are obtained for the whole period of observation, however, if the logarithm of concentration is plotted against the logarithm of time. No consistent difference was observed between a first and a second dye injection.

Curves for the cell plasma ratio usually bear no resemblance to those for dye concentration. As a rule, these ratios, which were 10 to 20 per cent above the pre-injection values, did not change progressively after the first sample (at one minute after completing the injection). In some experiments, the ratio increased progressively for several minutes after the injection was complete, a finding for which no explanation has been obtained.

These experiments have been repeated and confirmed by successive injections of dye and cells separately, to make sure that hemolysis in the dye-cell mixture did not interfere with the dye determinations.

The influence of hypothyroidism on plasma and liver protein concentrations. JAMES H. LEATHEN and ROBERT D. SEELEY (by invitation) *Bureau of Biological Research, Rutgers Univ.*

*New Brunswick, New Jersey* Hypothyroidism induced by antithyroid drugs will alter the normal plasma protein concentrations. However, when thiourea (0.5%) was used a body weight loss in excess of that lost by pair fed normal rats was noted so that the effect on the plasma proteins may have been the responses to a toxic effect. Therefore this problem has been reinvestigated using thiouracil.

Adult male rats were fed the stock diet plus 0.5% thiouracil ad lib and compared with pair fed normal controls after 20-25 days. A rise in plasma globulin concentration, total plasma protein and in NPN followed thiouracil feeding but plasma albumin concentrations simulated those of the controls. Despite a slight decrease in body weight resulting from a voluntary reduction in food intake, the livers from the thiouracil fed rats were significantly heavier than those from controls. Since the per cent water and protein remained unchanged, an increase in liver protein/100 gram body weight resulted.

Thyroidectomy, while inducing the same plasma protein changes as thiouracil, did not, however, induce a relative increase in liver weight when compared with pair fed controls 20 days after thyroid removal. The per cent water in the liver was unchanged and the per cent protein failed to exceed that of the controls, thus in the absence of a liver weight increase the amount of liver protein/100 gram body weight did not increase following thyroidectomy as it did with thiouracil over a 20 day period.

**Reactions of dairy cattle over a range of controlled temperatures and humidities.** DOUGLAS H. K. LEE and R. F. RIEK (introduced by E. F. Adolph) *Dept. of Physiology, Univ. of Queensland, Brisbane, Australia*. Jersey cows and calves were exposed to various controlled atmospheres of 85-110°F and 60-160 grains of moisture/cu ft air.

In the course of seven hours' exposure, the rectal temperature of calves rose more rapidly than that of milking cows. At lower air temperatures the calves reached higher equilibrium levels than milking cows, but at higher air temperatures they were similar. The respiratory rates of calves reacted much more rapidly than those milking cows, and reached higher equilibrium levels. A method has been devised of expressing the reactions of animals to such atmospheres both graphically and by equations. Humidity has a marked effect at high air temperatures upon the reactions of cows and to a less extent of calves.

With 14 repeated daily exposures to 105°F and 126 gr/cu ft the mean body temperature of milking cows during the exposure fell by 1°F, but respiratory rates were relatively unchanged.

With continuous exposure to 99.5°F and 126 gr/cu ft the rectal temperature of milking cows

rose steadily to 104.5°F on the second day, fell to 104°F by the fourth day and then rose to 105°F on the sixth day, whereas a dry cow reached a maximum of 102.7°F on the fifth day and improved rapidly thereafter. Under similar conditions calves rose steadily to 105.5°F on the seventh day, the females always being higher than the males.

Discontinuous exposure affected neither milk nor total butter fat production, but continuous exposure produced a marked fall in both, probably through the anorexia which forced withdrawal although a critical hyperthermia had not been reached.

**The peripheral vascular system and its reactions in scurvy, an experimental study.** RICHARD E. LEE and NINA ZWORYKIN LEE (introduced by Magnus I. Gregersen) *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* The study of the small mesenteric vessels of unanesthetized guinea pigs has been made possible by a technique using a local anesthetic for operative exposure. The gut and mesentery are maintained in a warmed chamber, bathed by a continual drip of warmed Ringer gelatin solution, and observed with the microscope.

In scorbutic animals, the mesenteric peripheral vascular system showed, (a) a hyporeactivity of the contractile vessels to topically applied epinephrine, (b) dilatation, and (c) sluggishness of blood flow. These conditions developed only in the muscular blood vessels distal to the pulsatile arteries, that is in vessels less than 100 to 125 micra in diameter. The changes were especially prominent in the small terminal collecting venules. On the other hand, the true capillaries of the scorbutic animals were of the same calibre as those of the controls. No abnormalities of the capillary wall were observed.

Spontaneous petechiae were not seen, but following direct trauma to the capillary bed (10 strokes of a small camel's hair brush) they occurred in 11 of the 23 scorbutic and in 2 of the 20 control animals. It should be noted that at least 85 per cent of these petechiae were located in the small collecting venules which drain the capillary bed. In this region, the dilatation and sluggish blood flow were also most marked.

The peripheral vascular hypotonia of scurvy may result from a scorbutic impairment of vasoconstrictive mechanisms [Aided by a grant from the Baruch Committee on Physical Medicine to Columbia University].

**Factors influencing an anaphylactoid reaction in the rat.** JACQUES LÉGER<sup>1</sup> (by invitation), GEORGES M. C. MASSON and J. LEAL PRADO<sup>2</sup>

<sup>1</sup> Fellow National Research Council (Canada), Medical Sciences

<sup>2</sup> Fellow Canada Brazil Fund

(by invitation) *Inst de Medecine et de Chirurgie experimentales, Univ de Montreal* It has been shown that in rats prearterial injection of egg-white produces an edema localized to the face, tongue and paws. Since the retention was probably connected with the proteins of egg white, experiments were conducted in order to determine which protein fraction was responsible for this effect. Rats were injected intraperitoneally with the following substances: crystalline egg white albumin, ovomucin, ovomucoid and chicken's blood serum. The latter substance has been used instead of conalbumin since chicken's serum albumin has been proven to be immunologically identical with that protein. Only ovomucoid was active.

The effects of various endocrine glands on this condition were investigated. Since thyroxine enhances the intensity of anaphylaxis in the rat, experiments were conducted in order to evaluate the effects of this hormone. Rats treated with a daily dose of 100 $\gamma$  of sodium thyroxinate received subsequently on the 12th day one intraperitoneal injection of 0.15 cc of fresh egg white. Within a few minutes, the animals presented a condition characterized by the following symptoms: decrease in spontaneous motility, dyspnea, weakness, cyanosis, coma and finally death. Similar experiments performed with the various fractions of egg-white showed that ovomucoid is also the causative agent of the shock-like condition.

Thyroidectomy delays the typical edema and decreases its incidence and intensity.

A pulmonary cardiovascular reflex in man. A LEVENDORFER (introduced by W. S. McCulloch) *From the Dept of Psychiatry, Univ of Illinois College of Medicine* Holding breath at the end of a forced inspiration causes a prompt fall in systolic and a less fall in diastolic blood pressure, accompanied by a slowing of the heart in which diastole is prolonged and the T wave is much diminished or isoelectric. The reverse of all of these changes occurs to a lesser extent on holding breath at the end of a forced expiration. All changes, particularly those of the T wave, are increased by the erect posture.

The accompanying changes in CO concentration of blood are not such as to account for any of these findings. They are in harmony with those of Schwiegl and of Daly and his coworkers on dogs wherein increased pressure in the pulmonary circulation was shown to give a fall in systemic blood pressure and slowing of the heart, both of which were prevented by section of the vagosympathetic nerves to the lung. [Aided by a grant from The Rockefeller Foundation.]

A photometric analyses of fibrin formation. JOSEPH LEIN (introduced by Robert Gaunt) *Dept of Zoology, Syracuse Univ and the Dept of Biology, Princeton Univ* The light scatter changes occurring during the clotting of fibrinogen by

thrombin were studied. It was found that the presence of non-clottable proteins increases the light scatter measurements. This fact is believed to indicate that extraneous proteins enter into the fibrin structure, being trapped in the process of fibrin formation.

Assuming the clotting of fibrinogen to be a polymerization reaction, a system of kinetics was developed based on first order reaction mechanisms. Making the assumptions (1)  $dN/dT = K_1F$ , (2)  $-dF/dT = K_2F$ , (3)  $LS = K_3(N - N_s)$ , the following equation can be derived:

$$\log \left( \frac{K_1 K_2}{K_3} \frac{F_0 e^{-K_2 T_s}}{F_0 - L_s} - L_s \right) = -0.434 K_1 T$$

$$\log \frac{K_1 K_2}{K_3} \frac{F_0}{F_0 - L_s}$$

where  $N$  = particle size,  $F$  = fibrinogen concentration,  $F_0$  = initial fibrinogen concentration,  $T$  = time,  $LS$  = light scatter,  $T_s$  = time when light scatter first occurs,  $N_s$  = minimum particle size that scatters light and  $K_1, K_2, K_3$  = constants defined above.

The equation was applied to the clotting of different concentrations of fibrinogen (range 0.2% to 0.04%) by the same concentration of thrombin. Calculated constants agreed with empirical constants with an average deviation of 6%.

Since the reaction is described by first order mechanisms, the polymerization process is thought to be independent of thrombin. The clotting of fibrinogen by thrombin is assumed to take place in two stages, activation and polymerization. In the first reaction thrombin activates some of the fibrinogen molecules. In the second reaction the activated fibrinogen polymerizes with the inactive fibrinogen forming progressively larger polymers, the state of activation not being lost in the process.

The mode of excretion of fructose by the dog. R. LEVINE and B. HUDDLESTON (by invitation) *Dept of Metabolism and Endocrinology, Research Inst, Michael Reese Hospital, Chicago, Illinois* The clearance of fructose by normal dogs was determined at plasma levels ranging from 2-200 mg/100 cc. Simultaneous creatinine clearances served as measures of the glomerular filtration rate. The  $T_m$  for fructose ranges from 40-60 mg per minute, for dogs weighing about 10 kg. Saturation of the mechanism for the reabsorption of glucose did not interfere with the reabsorption of fructose, pointing to separate tubular systems. However, phlorhizin lowers fructose reabsorption, in the same manner as it affects the handling of glucose by the renal tubule. [Aided by a grant from the Sugar Research Foundation.]

The comparative action of insulin on the disposal of intravenous fructose and glucose. R. LEVINE and B. HUDDLESTON (by invitation) *Dept of Metabolism and Endocrinology, Research Inst, Michael Reese Hospital, Chicago, Illinois* Previous work by Wierzechowski, and in our own

laboratory had indicated that the rate of entry of fructose into the metabolic cycle of the tissues is not influenced by the administration of additional insulin to normal animals, or its addition to tissues in vitro. The present study compares the disposal rate of fructose in normal and totally depancreatized dogs. The role of the liver was determined by comparing intact and hepatectomized animals.

Fructose in amounts from 0.3–2.0 grams/kg/hr injected i.v. is taken up at the same rate by untreated depancreatized dogs as by the normal control animals. The addition of insulin has no effect on the rate of fructose uptake.

The liver disposes of about 85 per cent of the injected fructose, and converts a part of it to glycogen and lactic acid.

The extrahepatic tissues remove fructose at  $\frac{1}{3}$  the rate of equal amounts of glucose.

In normal animals the blood glucose does not rise during or after fructose infusion. In untreated depancreatized dogs, despite the normal uptake of fructose, the blood glucose rises continuously during the infusion. Addition of insulin suppresses this glucose rise in depancreatized animals, without affecting the fructose disposal rate.

These results seem to indicate separate mechanisms for the initial glucose and fructose phosphorylations. Insulin exerts its action on the glucose mechanism exclusively. The relation of these data to the present scheme of intermediary metabolism of carbohydrates will be discussed [Aided by a grant from the Sugar Research Foundation].

**Modifications in plasma protein pattern (Tiselius electrophoresis technic) in adrenalectomized and adrenalectomized-hypertensive dogs.** LENA A. LEWIS and IRVINE H. PAGE. *From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio.* Plasma protein changes following adrenalectomy in dogs have been studied previously by chemical fractionation methods (1). Because of the importance of the adrenal glands in maintenance of normal blood pressure and of the finding of renin-substrate in the  $\alpha_2$  globulin fraction, the problem deserved reinvestigation using the Tiselius electrophoretic technic. Albumin,  $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ ,  $\phi$ , and  $\gamma$  globulins were estimated. Normal dogs and dogs made hypertensive by wrapping the kidneys in silk were adrenalectomized and various types of replacement therapy studied necessary to maintain blood pressure at pre adrenalectomy levels. Plasma was also tested in some cases for renin-substrate activity.

Following adrenalectomy when the dogs were well maintained on adrenal extract, there was slight decrease in albumin and a small increase in each of the globulin fractions. The  $\alpha_2$  globulin in 2 of the 4 dogs studied showed a relatively greater increase than did the other globulin fractions.

When the animals were in adrenal insufficiency, the  $\alpha_2$  globulin level was equal to or above the normal level in 3 of 4 cases.

During development of hypertension prior to adrenalectomy, the  $\alpha$  globulin increased. No consistent changes in the other fractions were observed. Following adrenalectomy, the hypertensive blood pressure levels were maintained when the dog was treated with adrenal extract or with compound A and desoxycorticosterone acetate. It was possible to restore the blood pressure to the pre adrenalectomy hypertensive level after allowing the animal to develop typical adrenal insufficiency. The plasma protein changes following adrenalectomy were similar to those observed in non-hypertensive dogs and showed renin substrate as well.

**Steady Potentials and Neurone Activity in Mammals.** B. LIBET and J. B. KAHN, JR. (by invitation). *Dept. of Physiology, The Univ. of Chicago.* Following findings on frog brain (B. Libet and R. W. Gerard, *J. Neurophysiol.* 4:438, 1941), the relationships between relatively steady electrical potential gradients and neurone function in mammals are being investigated. Preliminary observations, with a high input resistance amplifier (Victoreen tube) and galvanometer, mainly on cats under light ether, indicate the following:

"DC"-gradients, millivolts in size, exist between surface points of the cerebral cortex. Occasionally, 5–10 mV have been found between points 1 mm apart. DC gradients vary with time, and from cat to cat. There appears to be no consistent pattern of gradients, however, areas about the ecto-sylvian sulci appear generally negative to other areas, and the P.D. is less between analogous points of opposite hemispheres than between non-analogous points. The cortical surface is generally negative (1–10 mV) to calvarium bone. In a few animals followed after death, the cortex was positive to bone and this P.D. disappeared slowly over several hours.

Occasionally, a P.D. decreases, reverses polarity, and returns again—a change of 5–10 mV over a two-minute period. This indicates slow changes occur in brain, their significance must yet be worked out.

Shifts in apparent DC-gradient between sensory cortex and bone, of 0.2–0.3 mV, are observed with appropriate sensory stimulation, generally surface negative in the somesthetic area, surface positive in the acoustic. None could be elicited in the visual area. Strychnine increases these responses. The possibility that these responses are summated fast waves is yet to be analyzed.

Study of DC changes with other cortical activities, e.g., spreading waves, is proceeding.

**Pathways of conversion of butyrate carbon to rat liver glycogen.** NATHAN LIFSON, VICTOR



LORBER, WARWICK SAKAMI (by invitation) and HARLAND G WOOD *Dept of Physiology, Univ of Minnesota Medical School, Minneapolis and Dept of Biochemistry, Western Reserve Univ Medical School, Cleveland* Fasted rats were fed by stomach tube glucose and  $C^{14}$  labeled butyrate. The livers were extirpated 2-3 hours later, the glycogen isolated and degraded to determine the position of labeled carbon in the constituent glucose chains (Wood et al, J B C 159 475, 1945).

In the following, the notation,  $CH_3CHCH_2C^*OOH \rightarrow C-C-C^*-C-C$ , for example, indicates that glucose from liver glycogen isolated after feeding of  $CH_3CHCH_2C^*OOH$  contains isotope predominately in carbons 3 and 4.

#### Results

- (1)  $CH_3CHCH_2C^*OOH \rightarrow C-C-C^*-C^*-C-C$ ,
- (2)  $CH_3CH_2C^*H_2COOH \rightarrow C^*-C^*-C-C-C^*-C^*$ ,
- (3)  $CH_3C^*HCHCOOH \rightarrow C-C-C^*-C^*-C-C$

Discussion Previous work has shown  $C^*O \rightarrow C-C-C^*-C^*-C-C$  (CO fixation, Wood et al, loc cit). Therefore result (2) indicates that at least the alpha carbon of butyrate reaches liver glycogen by a pathway in addition to CO fixation.

Previous work has also shown (Lorber et al, J B C 161 411, 1945) that  $CH_3C^*OOH \rightarrow C-C-C^*-C^*-C-C$  and that  $C^*H_2C^*OOH \rightarrow C^*-C^*-C^*-C^*-C^*-C^*$ , from which it is inferred that, in all probability,  $C^*H_2COOH \rightarrow C^*-C^*-C-C-C^*-C^*$ . These findings with acetate are those expected from conversion of acetate carbon to glycogen precursors (pyruvate) via the tricarboxylic acid cycle. Results (1), (2), and (3) are all consistent with beta-oxidation of butyrate to 2 molecules of acetate. From  $CH_3CHCH_2C^*OOH$  and from  $CH_3C^*HCHCOOH$ , the glycogen ( $C-C-C^*-C^*-C-C$ ) resembles isotopically that from  $CH_3C^*OOH$ , from  $CH_3CHC^*HCOOH$ , the glycogen ( $C^*-C^*-C-C-C^*-C^*$ ) resembles that which  $C^*H_2COOH$  should yield.

Result (3) is inconsistent with omega-oxidation of butyrate to succinate, if succinate conversion to glycogen proceeds via pyruvate. By this pathway,  $CH_3C^*HCHCOOH \rightarrow COOH-C^*H_2-C^*H_2COOH$  (symmetrical molecule)  $\rightarrow COOH-C^*H_2C^*OCOOH \rightarrow C^*H_2C^*OCOOH \rightarrow C^*-C^*-C-C-C^*-C^*$ . Actually, however,  $CH_3C^*HCHCOOH \rightarrow C-C-C^*-C^*-C-C$ .

Comparison of rhythmic movements of breathing and progression: evidence for common mechanisms. RICHARD H LILLIE (by invitation) and ROBERT GESELL *Physiology Lab, Univ of Michigan, Ann Arbor* Progression movements of rear limbs of unanesthetized chronic spinal dogs showed striking resemblance to rhythmic movements of breathing as observed by Brown.

Study of these movements uphold view that principles of nervous integration previously applied to respiration might be profitably extended to spinal portion of nervous system.

Simultaneous observations were accordingly made on rhythmic movements of progression and breathing under the influence of carbon dioxide, asphyxia, and anticholinesterases physostigmine and prostigmine. It was noted that concentrations of  $CO_2$  (5 to 10%) which increased respiratory movements also increased frequency and amplitude of progression movements. Higher concentrations of carbon-dioxide tended to diminish frequency of progression movements despite accompanying increase of amplitude. Asphyxia produced changes in progression movements comparable to those of  $CO_2$ . Response of progression movements to  $CO_2$  was as prompt as that ordinarily observed for respiration.

Physostigmine augmented respiratory and progression movements. Leg movements, however, were not always as perfectly rhythmic as were respiratory movements. Effects of prostigmine on progression movements were in general like those of physostigmine but respiratory response was less marked.

Results indicate that the acid-humors electronic theory applies to nervous integration in spinal cord and to respiratory act and that concept of interaction of half centers (Brown) holds similarly for rhythmic flexion and extension, and inspiration and expiration of breathing. These conclusions agree with broader view that basic patterns of the mechanisms of nervous integration were laid down originally in the evolution of the nervous control of breathing.

The formation of acetylcholine in the developing retina of the chick embryo. V F LINDEMAN (introduced by Robert Gaunt) *Dept of Zoology, Syracuse Univ* The developing retina of the chick embryo provides a rather unique neural structure for the study of acetylcholine formation. The author has previously shown that the acetylcholine content of the developing chick retina reaches a maximum level of around 12 gamma per gram of tissue at approximately 19 days of incubation. This level is maintained until after the chick emerges from the shell when it falls to a new level with less than half this quantity of the ester (Amer J Physiol 148 1947).

The present study indicates a rather definite relationship between acetylcholine content and the ability of the retina to synthesize the ester during different stages of development. During the stages of maturation from the 12th to the 19th day the acetylcholine content builds up to a maximum. However, the ability of the tissue to synthesize acetylcholine progressively decreases over this same period. Thus when the acetylcholine



content is maximum its ability to synthesize is minimum. When the chick emerges from the shell and the content falls to a new level the rate of formation is again increased. The findings indicate that in the developing neurones of the chick retina the rate of formation of acetylcholine is limited by the amount of bound ester present in the cells at different stages of maturation.

**Changes in the human electroencephalogram produced by sodium cyanide.** B. S. LIPTON (by invitation) and F. A. GIBBS *From the Dept of Psychiatry, Univ of Illinois College of Medicine*. The electroencephalographic changes occurring in man with rapid intravenous injection of sodium cyanide vary with the dose. Small doses cause 8-10 per second waves while higher doses cause 8-10 per second waves followed by high voltage 2-3 per second activity. When still higher doses are used, the slow waves are followed by slower activity at  $\frac{1}{2}$  to 1 per second with a decrease in amplitude, which may proceed to complete flattening of the record.

The recovery phase follows an opposite time course. Flattening is succeeded by high voltage very slow waves and these by moderately slow waves which gradually increase in frequency until normal activity reappears.

This flattening can be regarded as an extreme form of slowing. If cyanide is given in sufficiently high dosage, sudden flattening occurs without preceding slowing. It is paradoxical, but nevertheless true, that with leads on the scalp the change produced by extreme interference with cortical oxygen metabolism is indistinguishable from an "attention response." This fact must be recognized in order to avoid serious confusion.

**Influence of body temperature and of temperature of traumatized tissues upon local edema and survival of dogs subjected to ischemic compression trauma of their hind extremities.** EDGAR L. LIPTON (by invitation), ADAM B. DENISON (by invitation) and HAROLD D. GREEN *Dept of Physiol and Pharm, Bowman Gray Sch of Med of Wake Forest Coll, Winston-Salem, N. C.* Dogs were traumatized by 6 hours of ischemic compression of both hind legs. Environmental temperature for the body was room temperature, compressed leg temperature was controlled by temperature of water circulated around legs. Animals divided into three groups: (I) hind legs warmed to approximately 38°C during period of compression, environmental temperature for body averaged 33°C until death, rectal temperature averaged 40.2°C; (II) hind legs warmed to approximately 37.5°C, environmental temperature 20°C until death, rectal temperature averaged 33°C; (III) hind legs at 24°C, environmental temperature at 33°C for 24 hours, rectal temperature averaged 38.8°C.

Survivals were as follows: (I) all 9 dogs died, average 6.2 hours; (II) 9 of 10 dogs died, average 12.4 hours; (III) 8 of 10 dogs died, average 14.9 hours. T value for difference between groups I and II was 1.89 and for difference between I and III was 2.69.

Average edema of traumatized legs, measured by immersion was: (I) 22.3, (II) 27.1, and (III) 15.0 ml/kg body weight. T value for difference between I and II was 0.99 and for difference between I and III was 1.16.

The differences in survival are statistically significant and indicate that cooling the body alone for 24 hours or cooling the legs alone for 24 hours or cooling the legs alone during the period of compression trauma prolongs the survival. The differences in edema are not statistically significant but it should be noted that the smallest occurred with the cooled legs and the greatest with warmed legs and cooled body. [Aided by grant number 543 from the Council on Pharm and Chem of the Am Med Assoc.]

**Diuresis in unanesthetized dogs following the intravenous injection of dog, human, or dialyzed human urine.** J. MAXWELL LITTLE *Dept of Physiology and Pharmacology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.* A previous report (Little, Hawkins and Green, Fed Proc 5:65, 1946) stated that repeated reinfusion of urine in dogs resulted in an increased urine flow. This is a true diuresis as shown by injecting 5 or 10 cc/kg of dog urine, adjusted to pH 7.4. Diuresis resulted with an average diuretic ratio ( $DR = \frac{\text{maximum rate}}{\text{control rate}}$ ) of 17.0 (14.5-21.0, 6 experiments). The average fluid recovery

(FR =  $\frac{\text{total urine flow corrected for control rate}}{\text{volume of fluid injected}} \times 100$ ) was 319% (206%-415%). For control a solution with the same urea and chloride concentration (NaCl) as the urine was injected. DR = 5.9 (4.1-7.4, 6 experiments), FR = 94% (45%-135%). In identical experiments with human urine DR = 11.7 (5.0-25.3, 5 experiments, 2 donors), FR = 235% (130%-310%). control DR = 5.4 (3.6-10.7), FR = 93% (12%-193%). In identical experiments, human urine dialyzed against distilled water until neutral to litmus and negative for chloride (sg = 1.001) DR = 9.4 (5.0-13.8, 6 experiments, 3 donors), FR = 262% (172%-385%), control experiments with distilled water failed to affect the rate of urine flow except in one case when FR = 17%. Urine and dialyzed urine from one subject resulted in antidiuresis for 1-3.5 hours in two dogs. It is concluded that human and dog urine contain a non-dialyzable diuretic factor.

**Pathology in suddenly decompressed rats**

R B LIVINGSTON (by invitation), S GLIFAN and L F NIMS *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn* Unanesthetized rats were suddenly decompressed in a chamber from a simulated altitude of 20,000 feet to altitudes ranging up to 75,000 feet. The half time of decompression for most of the experiments was about 0.2 second. Pathological studies were made after recompression to sea level. Grossly visible bubbles were infrequently found. They tended to occur more often in the veins of rats decompressed to above 50,000 feet. None were seen when the half time of decompression was shortened to less than 0.1 second. Frequent hemorrhages into the cochlea were noted. The lungs showed pathology varying from diffuse petechial hemorrhages and edema to massive consolidation with blood. Rats dying at altitudes above 50,000 feet tended to have completely consolidated, liver like lungs which did not float in water. In these rats, the pulmonary veins and left auricle were collapsed, whereas the right side of the heart, the great veins, liver, spleen, kidneys and other organs showed evidences of passive congestion. These results suggest that nearly complete arrest of blood flow occurs in the damaged pulmonary bed. A few rats, quickly recompressed before respiratory failure occurred, were alive when removed from the chamber. Some of these surviving a few days showed signs of extensive renal damage in addition to pulmonary complications. [Investigation carried out under Contract W-33 ac 14507 (Right Field) between the Army Air Forces Air Materiel Command, and Yale Univ.]

**Pattern of monosynaptic reflex connection between certain muscles of the ankle and digits** DAVID P C LLOYD *Labs of The Rockefeller Inst for Medical Research, New York* Reflex interaction of afferent volleys from specific muscles of the leg and foot has been studied, employing monosynaptic reflex discharge of a given muscle as test, and observing the effect upon it of afferent volleys arising in other muscles. Conditioning of the test reflexes was plotted against the relative arrival time at the cord of conditioning and test afferent volleys. Interaction at intervals of less than 0.5 msec indicates the presence between muscles of direct reflex interconnection, facilitatory or inhibitory. In consequence is revealed the grouping of muscles into "myotatic units" (J Neurophysiol 9:439, 1946)

**Myotatic Unit of the Ankle** Facilitation obtains between the monosynaptic reflex arcs of the several heads of Triceps Surae, and between those of Tibialis Anterior and Extensor Longus. Tibialis Anterior and Extensor Longus are linked to the heads of Triceps by inhibitory connection.

**Myotatic Units of the Digits** Extensors Longus and Brevis possess facilitatory interconnection as

do Flexor Brevis and fractions of Plantaris. Extensor Longus and Brevis connect with Flexor Brevis and Plantaris by inhibitory pathways. The heads of Flexor Longus interact by facilitation, and are inhibited from Extensors Longus and Brevis.

Interest attaches to the participation of Extensor Longus in the myotatic units of both ankle and digits, reflecting that muscle's dual role as ankle flexor and dorsiflexor of the digits. The association of Plantaris with Flexor Brevis, in the cat, is an expression of the "in series" relationship of the two muscles. Tibialis Posterior is independent of all the muscles named.

**Relation of electrogram to mechanogram in mammalian skeletal muscle in different conditions** G N LOOFBOUROW (introduced by E Gellhorn) *Laby of Neurophysiology, Univ of Minnesota* The frequent assumption that E M G amplitude corresponds with contraction force is brought into question by abnormally large E M G's in muscles weakened by poliomyelitis and by the probability that routinely observed spikes are only indirectly associated with contraction.

**I Indirect stimulation of tibialis muscle (cat)** Considerable independence of E M G and mechanogram exists with indirect stimulation. The E M G is virtually constant with considerable variation in direct or after-load in twitches and tetani. The E M G increases slightly with increased initial length without proportionality to tension. Isometric tension increases with greater frequency of stimulus without increased E M G amplitude. At constant initial length, great tension may develop isometrically while the E M G is no greater than in an isotonic contraction with small load. E M G and mechanogram usually diminish together in fatigue, but in some cases considerable diminution in twitch contraction height occurs with constant potential amplitude.

**II Cortical stimulation** E M G increases directly with mechanogram as intensity, frequency, or direct load increases. Marked increases in E M G and isometric tension accompany increased initial length. Stretching muscle during isotonic contraction increases E M G much more than when stimulation is indirect.

**III Voluntary contractions** Increased isotonic or isometric loads result in increased amplitude of E M G in contrast to experiments on nerve-muscle preparation. It is suggested that results with voluntary or cortical excitation differ from those found in nerve muscle preparations because in the former case the CNS exerts control over the number of units activated and frequency of discharge. [Aided by a grant from the National Foundation for Infantile Paralysis.]

**The renal reabsorption and excretion of inorganic sulfate** W D LOTSREICH (introduced by R F Pitts) *Dept of Physiology, Syracuse Univ*

*College of Medicine, Syracuse, New York* The renal reabsorption and excretion of inorganic sulfate has been studied in ten experiments on two trained female dogs Plasma sulfate was varied from 1.4 to 12.2 mM/L by the intravenous infusion of sodium sulfate The rate of glomerular filtration was measured by the creatinine clearance Inorganic sulfate was determined on trichloroacetic acid filtrates of plasma and urine by alkalimetric titration of a purified precipitate of benzidine sulfate

At plasma sulfate concentrations below 1.5 mM/L reabsorption of sulfate from the glomerular filtrate was essentially complete At plasma sulfate concentrations above 2.0 mM/L gross excretion of sulfate occurred, and the rate of tubular reabsorption of sulfate became essentially constant and independent of plasma concentration, averaging 155 mM/100 cc of glomerular filtrate [*Aided by grants from the U S Public Health Service and the John and Mary R Markle Foundation*]

The role of amino acids in the renal tubular secretion of ammonia W D LOTSPEICH (by invitation) and R F PITTS *Dept of Physiology, Syracuse Univ College of Medicine, Syracuse, New York* A representative number of amino acids have been administered to acidotic dogs by intravenous infusion, and the rates of tubular secretion of ammonia and tubular reabsorption of amino nitrogen measured at a series of comparable plasma amino nitrogen concentrations It has been found that there exists a correlation between the capacity of an amino acid to increase ammonia secretion *in vivo*, and the susceptibility of that same amino acid to oxidative deamination *in vitro* by renal amino acid oxidases This has led to the conclusion that amino acid oxidases are concerned in the intact animal with the reactions of ammonia synthesis and secretion by the kidney It has been further shown that there exists a correlation between the extent to which an amino acid can increase ammonia secretion and the extent to which that same amino acid is reabsorbed by the renal tubules Two possible explanations for this correlation present themselves Either 1) the physical characteristics of the several amino acids determine their rates of penetration into the tubular cell from both tubular urine and peritubular blood, or 2) some common chain of intracellular reactions, involving amino acid oxidases, participates in both tubular functions of ammonia secretion and amino nitrogen reabsorption [*Aided by grants from the U S Public Health Service and the John and Mary R Markle Foundation*]

On some physiological effects of anticholinesterases CHARLES R LOWE (introduced by Robert Gesell) *Physiology Lab, Univ of Michigan, Ann Arbor* In the light of Nachmansohn's theory that conduction of the nerve impulse by the neuraxon is a cholinergic process, it seemed

advisable to study further the effects of various anticholinesterases (physostigmine, prostigmine, DFP, strychnine and carbon dioxide) Muscle nerve and muscle preparations of the frog were used Results 1 Exposure of a segment of the nerve trunk to these anticholinesterases resulted in a diminution or abolition of response of the muscle to indirect stimulation 2 Exposure of the entire muscle (fibers, terminal nerve branches and motor end-plates) to similar concentrations of anticholinesterases resulted in greater reduction of muscle response to indirect stimulation 3 Exposure of curarized sartorius muscle to anticholinesterases resulted in a reduced response to direct stimulation of the muscle 4 Exposure of curarized chronically denervated sartorius also resulted in reduced response to direct stimulation of muscle Result of procedure (1) can be interpreted as supporting Nachmansohn's theory The results of procedures (3) and (4) suggest the possibility that a cholinergic process could participate in the conduction of impulses in muscle fibers It is conceivable that the enhancing effect of impulse generation produced by anticholinesterase acting at the synapses of the dendrites and cell body of a chain of neurons could be partially or completely neutralized by a simultaneous impairment of impulse conduction by their neuraxons Interpretation of central action of anticholinesterases could, therefore, be more involved than is generally appreciated

Man's tolerance to positive acceleration in different orientations of the body DOUGLAS W LUND (introduced by H M Sweeney) *Aero Medical Lab, Air Materiel Command, Wright Field, Dayton, Ohio* The "black-out" levels, and other end-points, were determined for the conventional seated position on a series of subjects The centrifuge methods used have been described previously A mean black-out level of 4.2 g was obtained for this group

Using the same techniques of light response and centrifuge operation, the attitude and position of these subjects were varied with respect to the directional axis of radial acceleration Accelerometer readings were taken at the heart level At least two series of runs, and ten subjects were used to determine tolerance in each orientation Conditions of the 15-second centrifuge runs, with resultant mean black-out levels obtained, were as follows With the subject at rest, or "zero g," extended on the centrifuge, feet directed peripherally resting on a foot board, prior to centrifugation, black-out occurred at 1.9 g, or at 2.2 g when the subject's weight was supported in parachute harness (The use of a G3A anti-blackout suit increased subject tolerance from 1.9 g to 2.8 g) With the subject extended as above, but exposed to two or more minutes of centrifugation to 1 g prior

to rapid increase of g load, black-out occurred at 30 g. With the subject placed in the conventional seated attitude, except lying on his back in a seat until the moment of radial g application, black out occurred at 31 g.

On a basis of these findings, an orthostatic as well as positional factor must be considered in explaining the physiology of man's tolerance to positive acceleration. A loss of tolerance due to retarded venous flow lowering cardiac output is suggested.

**Thermoelectric recording of ice formation and of vitrification during ultra-rapid cooling of protoplasm.** B. J. LUIET and P. M. GLENNIE (by invitation) *Dept. of Biology, St. Louis Univ. and Biodynamica Lab., St. Louis, Mo.* When the water content of some colloidal or carbohydrate solutions is not higher than about 30% of the total weight no water can be made to crystallize out of such solutions by a lowering of temperature, even when cooling is very slow. The same is true of the protoplasm of some organisms that support desiccation such as mycetozoa. With higher water contents the formation of ice occurs at low cooling velocities but is inhibited at high. The influence of the cooling velocity was studied on photographically recorded cooling curves obtained with a thermocouple connected to a string galvanometer. One junction of the thermocouple was inserted in a droplet of the solution being studied or in a speck of protoplasm, which was immersed in liquid nitrogen in a layer 0.1 mm thick and about 3 sq mm in area, held between two thin glass slips. Under these conditions, the cooling velocity in the absence of crystallization was about 200 degrees per second. On curves obtained at such cooling velocities with sucrose solutions containing 80% water, or with active mycetozoan plasmodia, the freezing plateau, caused by the release of the heat of crystallization, was well observable, while it vanished from the curves obtained with solutions which still contained 50% water, or with partially desiccated plasmodia which were still of a pasty consistency.

**Effects of allovan administration in the calf.** ESTHER L. MCCANDLESS (by invitation) and J. A. DYE *Dept. of Physiology, Cornell Univ., Ithaca*

Intravenous administration of allovan to two month-old calves produced renal damage and mild disturbances in carbohydrate metabolism. Calf 1 received 65, 100, 150, and 175 mg per kg at 4, 6, and 22 day intervals, calf 2 a single dose of 150 mg per kg. The glycemic response was diphasic, no initial hyperglycemia occurred in either animal. The hypoglycemic phase with doses of 175 and 150 mg in calves 1 and 2, respectively, was severe and prolonged. Carpopedal weakness, tachycardia, hyperpnea, excessive salivation, ataxia, and circus movements typical of hypoglycemic convulsions

were observed 8, 13, 16, 20, 22, and 27 hours post-injection in calf 2. The blood glucose varied from 18 to 22 mg per 100 ml. Rapid recovery followed intravenous glucose injection.

In calf 1, transient hyperglycemia and persistent glycosuria were produced by the 100 mg dose, similar hyperglycemia and a temporary decrease in intravenous glucose tolerance occurred after 150 mg, increased glycosuria, slight ketonuria, and decreased glucose tolerance (still present after 143 days), oliguria, nitrogen retention, and persistent azotemia followed the 175 mg dose. Blood glucose and urinary nitrogen excretion returned to normal in this animal.

150 mg per kg was fatal to calf 2 in 44 hours. Anuria was present until death. Ascites was prominent. Histologically, no hepatic damage was demonstrable, complete coagulation necrosis of the renal tubules and marked pancreatic islet destruction were observed. The terminal hyperglycemia was 275 mg per 100 ml. [Aided by a grant from the Gans Fund of Bethany College, Bethany, W. Va.]

**The thyroid gland of the smallest mammal.** J. F. MCCLENDON and Wm. C. FOSTER (by invitation) *Hahnemann Medical College, Philadelphia*. Since some investigators have had difficulty in determining iodine in the thyroid glands of young or small individuals, we thought it might be of interest to determine iodine in the thyroid gland of the smallest mammal, the shrew. A pair of shrews, *Blarina brevicauda*, Say, were caught in January. The male weighed 17.2 grams and the female 13.2 grams. The thyroid glands were so small that we combined them for analysis. The two contained 0.5 microgram of iodine. Evidently one of them contained not over 0.25% of iodine which we believe is the smallest amount in any mammal investigated. Yet this thyroid is large enough to regulate the body temperature of the shrew in winter.

**Origin and distribution of some long spinal reflex effects on crural muscles.** A. K. MCINTIRE (by invitation) and DAVID P. C. LLOYD *Labs. of The Rockefeller Inst. for Medical Research, New York*. Afferent volleys arising in the forelimb inhibit some motoneurons of the ipsilateral lumbo-sacral cord with a latency sufficient for conduction and a single synaptic relay in the cervical cord, and facilitate lumbo-sacral motoneurons only after further delay of several msec. (*J. Neurophysiol.*, 1942, 5: 435). The afferent fiber groups mediating these effects, and some of the motoneurons affected have been identified by stimulation of cutaneous or muscle nerves in the forelimb with graded shocks, and by the use, for testing, of monosynaptic reflex discharges of specific hind-limb muscles.

Group I afferent fibers, confined to muscle nerves and subserving myotatic reflexes, appear to have no effect on motoneurons of crural muscles.

Low threshold Group II fibers, the largest fibers of cutaneous nerves, are responsible for the early inhibition of lumbar motoneurons. Tests of a number of motor nuclei reveal this inhibition only among the motoneurons of Flexor Longus Digitorum (Tibialis and Fibularis). The inhibition is unaccompanied by conditioning of the antagonists, Extensors Longus and Brevis.

Group II and Group III afferent fibers provoke generalized facilitation of crural extensor motoneurons, the afferent threshold being higher and the latency 4-6 msec longer than for the inhibition of Flexor Longus. The facilitation of hind-limb extensors develops *pari passu* with reflex flexion in the stimulated forelimb, and may be regarded as a postural adjuvant of that flexion.

Monosynaptic reflex discharges pertaining to crural flexors are little altered by forelimb afferent volleys, but multineuron reflexes in the hind-limb are clearly inhibited, apparently at the interneuronal level.

**The actions of certain drugs on an actomyosin-ATP system.** A. R. McINTYRE and IRVIN BRAVERMAN (by invitation) *Dept of Physiology and Pharmacology, Univ of Nebraska, College of Medicine, Omaha*. Actomyosin threads, prepared from rabbit muscle (Szent-Gyorgyi's method), were cut to a length of 2 mm, suspended in 0.05 M KCl solution on a hollow-ground slide, and observed under a microscope equipped with a calibrated ocular micrometer. ATP, added to the suspending fluid, caused an average decrease in length of 30% in 60 seconds.

The following substances, when added to the suspension in concentrations ranging from 0.003 M to 0.017 M, did not modify the effect of ATP: acetylcholine bromide, atropine sulfate, nicotine alkaloid, ephedrine hydrochloride, prostigmine bromine, physostigmine salicylate, sodium fluoride, veratrine sulfate, pilocarpine hydrochloride, morphine sulfate, sodium iodoacetate, alpha-tocopherol phosphate, quinine methochloride, and caffeine alkaloid.

Sodium heparin, in 0.017 M concentration, completely prevented contraction. In 0.003 M concentration, it allowed a decrease in length of only 6%. Copper sulfate, too, lessened the degree of contraction. D-tubocurarine chloride, in 0.003 M concentration, did not affect contraction, but in 0.017 M concentration, caused the thread to disintegrate. Quinine methochloride, which has a curariform effect, when used in the same concentrations as the d-tubocurarine, did not affect contraction. Iodoacetic acid (pH 3.2) caused disintegration, but sodium iodoacetate (pH 7.08) had no effect. However, the pH *per se* was probably

without marked effect, for the effects of veratrine sulfate (pH 5.4), alpha-tocopherol phosphate (pH 6.8), and alpha-tocopherol phosphate (pH 10.1) differed not at all. Caffeine alkaloid had no effect on the contraction of the thread, but caffeine citrate and theobromine salicylate, the same concentrations, caused disintegration.

**Observations on the dilution principle of relative serum volume estimation.** PAUL L. McLAIN and C. H. WILLIAM RUHE (by invitation) *Dept of Physiology and Pharmacology, School of Medicine, Univ of Pittsburgh*. In order to assay the experimental errors involved in certain applications of the dilution technique for estimation of relative serum volumes in blood, 10 method variations, each in 10 standard dilutions, were applied to known volumes of 22 samples of beef serum. Serum volumes thus estimated were compared with the known original volumes, and the errors of estimate computed. Methods included measurement of specific gravity, total serum nitrogen, serum protein from serum nitrogen, and heat-coagulable, non-chloroform, non-water-soluble solids. The later 2 fractions were also estimated from specific gravity. Significant differences were observed among the methods. The mean error of estimate varied with the particular method from 3.4 to 8.8 per cent of the true volume, maximum errors reaching 50 per cent. The lowest mean error was found with the gravimetric "solids" method. Within certain limits, degree of dilution influenced the reliability of the estimates. The best dilutions involved 4 or more volumes of diluent for each 10 volumes of serum. The most reliable method, in the most favorable dilution range, had a mean error of  $2.4 \pm 0.15$  per cent. However, the distribution of errors for all methods indicated that the techniques employed were not well adapted to such precise volume estimation as is required for correction of the centrifugal hematocrit. Further, for every method, the mean volume estimates exceeded the correct values, an indication that the methods employed, when applied to whole blood, would favor high relative serum volumes and low corpuscle volumes.

**Comparison of centrifugal hematocrit techniques.** PAUL L. McLAIN *Dept of Physiology and Pharmacology, School of Medicine, Univ of Pittsburgh*. As part of a general study on relative corpuscle and serum volumes, 3 centrifugal hematocrit methods were compared for 10 samples of whole beef blood and for 3 standard dilutions of each sample with its own serum. Daland tubes were subjected to approximately 7500  $\times$  G until constant sediment volumes were obtained. Wintrobe and ordinary, tapered, 15-ml centrifuge tubes were spun at about 1400  $\times$  G for one hour. The methods yielded slightly different but statistically indistinguishable means for the entire series and at

each dilution level. As to quantitative detection of dilution, however, the Daland method showed a mean error of 0.95%, regular centrifuge tubes 1.95%, and Wintrobe tubes 2.05%. Regarding distribution of these errors, the methods had the same general order of merit, all errors with the Daland tubes being less than 3% of the expected value, an accuracy attained in about three fourths of the Wintrobe and regular centrifuge tests. Average deviations from the Daland values, based on relative volumes of packed cells, were 2.20% for Wintrobe and 3.53% for regular centrifuge tubes. For these deviations, the Wintrobe readings showed the better frequency distribution. Results for regular centrifuge tubes exceeded the corresponding Daland values in 100% of observations, Wintrobe tubes in about 75%. Degree of dilution did not significantly affect the relative differences between Daland and other readings.

The oxygen consumption during the assimilation of nitrogen sources by the bacterium *Serratia marcescens* DOROTHY J. McLEAF (by invitation) and KENNETH C. FISHER, *Univ. of Toronto, Toronto, Canada*. During the assimilation of ammonia by the bacterium *Serratia marcescens* the rate of oxygen consumption is higher than in the absence of such assimilation. After reaching this higher level the rate of oxygen consumption increases exponentially and the ammonia is taken up from the medium. When the ammonia is exhausted the rate of oxygen consumption falls to a lower rate typical of resting cells. Since the lower rate is always a definite percentage of the higher one, the resting rate corresponding to any growing rate can be calculated. Any oxygen consumed, in excess of the amount expected for resting cells, must be associated with the assimilation of ammonia. This quantity of oxygen has been calculated and compared to the quantity of ammonia assimilated. By changing the nitrogen and carbon sources it has been found that, while the excess oxygen consumed in assimilation is relatively constant for one set of conditions, it may vary three fold as the carbon and nitrogen compounds which are supplied are changed.

Respiratory responses resulting from varying degrees of temporary pulmonary artery occlusion in the anesthetized dog CLARENCE A. MAASKE, DONN L. SMITH<sup>1</sup> (by invitation) and ROBERT F. RUSK (by invitation), *The Dept. of Physiology and Pharmacology, the Univ. of Colorado School of Medicine, Denver*. Partial occlusion of the pulmonary artery for short intervals in intact, unanesthetized dogs produces an increase in amplitude and/or rate of respiration during the period of occlusion. Respiratory responses to pulmonary artery occlusions, however, are more variable in acute experiments upon anesthetized dogs.

Pulmonary artery occlusions were produced in anesthetized dogs by exterior control of an adjustable clamp following closure of the chest and reduction of the surgical pneumothorax. Restriction of pulmonary blood flow usually, but not invariably, produced an increase in rate of respiration which appears to correlate with the extent of increase of central venous pressure, the relation of respiratory changes to the decrease in arterial blood pressure during occlusion is not as intimate. Bilateral vagotomy abolishes the respiratory response resulting from partial pulmonary artery occlusion.

Rapid infusion of isotonic saline via the right external jugular vein during periods of partial occlusion of the pulmonary artery was not always effective in causing respiratory changes. In the anesthetized dog a temporary increase of right heart and central venous pressures within certain limits, and without augmentation of pulmonary blood flow, may result, but not invariably, in an increase of respiratory rate.

Phytotoxic reactions of normal and irradiated blood sera DAVID I. MACHT and MARCUS OSTRO (by invitation), *Depts. of Pharmacology and Radiology, Sinai Hospital, Baltimore*. Studies on phytotoxic reactions of blood sera by one of the authors, for over 20 years, on seedlings of *Lupinus albus* have established that the root growth in 1% normal serum of all higher animals including man under standardized conditions in plant physiological saline is 70% to 75% of growth in normal Shive solution. Certain clinical conditions, however, produce characteristic phytotoxic effects measurable quantitatively as follows:

Growth in normal plant physiological solution	100%
Growth in 1% normal serum	70%-75%
Growth in 1% menstrual serum	52%
Growth in 1% pernicious anemia serum	44%
Growth in 1% pemphigus serum	59%
Growth in 1% leprosy serum	47%
Growth in 1% trachoma serum	48%

The present report describes the influence of various radiations on the phytotoxic reactions of sera. Exposure in quartz cells to a Kromayer mercury vapor lamp produces no change in normal serum nor in the sera of leprosy, trachoma, and pemphigus, but these rays increase the toxicity of menstrual serum, and completely detoxify the blood of pernicious anemia, the most effective wave lengths being those of 3130 and 2967 Angstrom units. Roentgen rays filtered through 1 mm. aluminum and 2 mm. copper rendered normal and menstrual sera more toxic, produced no change in vitro of leprosy and trachoma sera, but detoxified the sera of pernicious anemia and pemphigus. Such detoxification of pemphigus blood also followed deep X-ray therapy over the liver and spleen in clinical patients and eight severe cases of

<sup>1</sup> Life Insurance Medical Research Fellow

pemphigus have been successfully treated with small doses in this way. Recently it was found that blood sera of all psychotic patients, organic and functional, are very poisonous for plants and these sera are detoxified in vitro by as little as 90r of the above mentioned filtered gamma rays. Further research on this subject is in progress.

**Influence of X-rays on the thromboplastic and phytotoxic properties of penicillin and streptomycin** DAVID I. MACHT and MARCUS OSTRO (by invitation) *Depts of Pharmacology and Radiology, Sinai Hospital, Baltimore*. One of the authors described elsewhere the inhibitory properties of penicillin on the root growth of *Lupinus albus* seedlings (Federation Proceedings, March, 1946) and again in these Proceedings the thromboplastic properties of antibiotics. In the present research experiments were made on the influence of X-ray radiations on penicillin and streptomycin solutions on the above two properties. Solutions of amorphous and crystalline penicillin were exposed to X-rays filtered through 1 mm aluminum and 2 mm copper operated on 200 kilo volts with a current of 20 milliamperes target at 50 cm, the doses used ranging from 90 to 180 r. Such solutions were more toxic for the growth of seedlings and when injected into cats and rabbits were more thromboplastic for the whole blood than the results obtained with non-irradiated penicillin. The inhibition of root growth was 10% to 20% greater with irradiated penicillin and streptomycin solutions. Similarly coagulation time of whole blood was much shorter after injecting the irradiated solutions of the antibiotics. These findings on plants prompted an inquiry as to whether the bacteriostatic and chemotherapeutic properties of penicillin may also be potentiated by irradiation. Such experiments are now in progress by the authors in conjunction with Drs. Lawrence Smith and Jerome Martin of the C. S. C. Research Laboratories.

**Influence of antibiotics and sulfonamides on the growth of yeast** DAVID I. MACHT *Dept of Pharmacology, Sinai Hospital, Baltimore*. The author has already reported the marked toxicity of penicillin for *Lupinus albus* seedlings (Federation Proceedings, March 1946). As little as 0.1 Oxford unit of penicillin can be easily detected in blood serum by plant physiological methods. The same is true of streptomycin. In the present research an inquiry was made whether microscopic plants such as yeast would act in the same way, using sugar fermentation as an indicator. 4% emulsions of *Saccharomyces Cerevisiae* was employed, 1 cc of the emulsion being mixed with 1 cc of drug solution for one hour. Sucrose or dextrose solutions 10% were added to make a total volume of 10 cc and the whole placed in fermentation tubes and left in a warm room at 76°F. In two hours

active fermentation was observed with evolution of CO<sub>2</sub> gas in control solutions. Surprising to find, penicillin even in concentrations of 200,000 units to 1 cc yeast emulsion did not inhibit the growth of yeast but actually stimulated it as compared with the controls. The same was true of streptomycin 30 mgs per 10 cc. Three sulfonamides, sulfadiazene, sulfamerazine, and sulfathiazole also did not inhibit yeast growth even in concentrations of the drugs 1 to 100. On the other hand, controls with sodium borate and sodium salicylate gave marked inhibition. The explanation of the above phenomenon lies probably in the fact that the antibiotics inhibit the growth of bacteria contaminating the yeast and thus promote the growth of yeast (Cf P. P. Gray and A. D. Kazin, Wallerstein Lab. Communications, August 1946). Botanically speaking the antibiotics are *schizomycetostatic* but not *ascomycetostatic*.

**Thromboplastic Properties of Penicillin and Streptomycin** DAVID I. MACHT *Dept of Pharmacology, Sinai Hospital, Baltimore*. Moldavsky and associates reported acceleration of blood coagulation in patients injected with penicillin (Science 1945, volume 102, page 38). Their clinical findings were confirmed by Macht and Ostro on human beings, except that they found, hemophiliacs do not respond with shortening of coagulation, after penicillin injections. In the present investigation a large number of experiments (200) were made on rabbits and cats. Amorphous penicillin of all brands markedly shortened coagulation time even with doses as low as 100 Oxford units per kilo. This effect supervenes usually within 30 minutes, but lasts for several hours. Crystalline sodium penicillin (C. S. C.) consisting mostly of penicillin G is much less active as a thromboplastic agent. For this reason the 4 active principles were examined separately. Penicillin X is the most thromboplastic, reducing coagulation time, sometimes from 15 minutes to 40 seconds, within half an hour after injection. A close second is penicillin K. Penicillin G is much less thromboplastic while F is the weakest of all. It is remarkable that the living body can take care of such potent thromboplastic agents without thromboembolic accidents. Nevertheless, the above properties should be born in mind in clinical practice.

**Influence of penicillin and streptomycin on the behavior of rats** DAVID I. MACHT *Dept of Pharmacology, Sinai Hospital, Baltimore*. Clinical reactions from penicillin and streptomycin are being reported, among them convulsions after penicillin and disturbances of hearing after streptomycin (cf Arch. Neurol. Psychiat., 56: 184, 1946). To study the subject scientifically the author investigated experimentally the neuromuscular and psychological responses of white rats after these drugs. The methods employed are described



in a similar study with sulfonamides (Macht D I, *Experimental Medicine and Surgery*, 1943, volume 1, page 260) Studies were made (1) on the behavior of rats in a circular maze giving data on neuromuscular activity and on discrimination or "choice" reactions, (2) on the coordination of rats walking over a tightly stretched horizontal rope, (3) on the neuromuscular work of rats climbing a vertical rope Both penicillin and streptomycin produced a marked depression by all three tests, when injected either subcutaneously or intraperitoneally The doses ranged from 5,000 to 20,000 Oxford units per adult rat weighing 200 gms Amorphous penicillin was more depressant than the crystalline sodium salt of penicillin (CSC) but depression was also produced by pure penicillin G alone Streptomycin was not more toxic than penicillin in the above respects In all experiments with both antibiotics the animals recovered after two or three days The most interesting finding was the development of a tolerance or resistance to the antibiotics so that rats which had been used several times no longer were much affected by subsequent injections

**Autonomous spinal responses to thermal stimuli:** A study of spinal man MARTIN B MACHT (introduced by H S Belding) *The Quartermaster Corps, Climatic Research Laby Lawrence, Mass*, and *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore, Md* The author has previously reported experiments demonstrating, in chronic spinal cats, the presence of certain responses to thermal stimuli mediated through the isolated spinal cord<sup>1</sup> To gain further information regarding the functional capacity of the cord, similar investigations have been conducted on spinal men at Cushing Veterans' Administration Hospital Six volunteers with anatomically proven complete transections of the cord and thirty with physiologically complete transections at lower cervical to upper lumbar levels have been studied

Immersing the lower extremities of spinal men in water of body temperature produces no observed effect When the foot is immersed in water of certain temperature levels above or below that of the foot, a withdrawal response is evoked The degree of response varies from hallux-extension with fanning of the toes to complete withdrawal with flexion at knee and hip In "cold" water immersion, the threshold for the response is dependent upon a gradient between the temperature of the water and that of the foot, and the receptors involved are probably end-bulbs of Krause However, in "hot" water immersion, threshold for the response is quite high (approximately 50°C), and relatively constant regardless of foot tempera-

ture, the receptors involved are probably free nerve endings

These responses to thermal stimuli were observed only in subjects who had recovered from spinal shock and possessed intact peripheral nerves Motion pictures demonstrating these reflexes have been filmed

**The relation of stomach shape to emptying time** S H MACHT (by invitation), M H F FRIEDMAN, and B H MALONE (by invitation) *Depts of Radiology and Physiology, Jefferson Medical College, Philadelphia, Pennsylvania* The subjects included 51 medical students, student nurses and college personnel who were not known to have either gastro intestinal or respiratory tract disease Only 5 subjects were over 25 years of age The test meal consisted of 15 grams cooked oat meal and 100 grams barium sulfate made up to 200 cc with water The meal was taken in the fasting state and no food, fluids or smoking were allowed during the observation period Serial fluoroscopic examinations were made with the subject in the erect position On the basis of the position and outline shown within 5 minutes after the ingestion of the meal, 24 cases were designated as having a stomach of steer-horn shape, 23 fish-hook shape, and 4 miscellaneous

Complete emptying of the steer horn type stomach occurred in less than two hours in 44 per cent of the cases and in less than 3 hours in 56 per cent In contrast, the fish hook type of stomach emptied in less than two hours in 13 per cent, during the third hour in 43 per cent, and after three hours in 44 per cent of the cases Emptying was complete in less than 2 hours in four subjects with the so-called "cascade" type of stomach

No distinct correlation was found between the height of the individual and the gastric emptying time No difference in emptying rates were observed between the two sexes

**The effect of pulmonary congestion on distensibility of the lung** I MACK (by invitation), M GROSSMAN (by invitation), and L N KATZ *Cardiovascular Dept, Research Inst, Michael Reese Hospital, Chicago, Illinois* The effect of congestion on distensibility of the lung was studied both in the isolated lung and in the intact animal The distensibility was first determined in the relatively bloodless isolated lung by inflating the lung with known volumes of air and determining the corresponding increments in plethysmographic and intratracheal pressures By plotting the pressure changes in the plethysmograph and the volume of air added to the lung against the pressure changes in the trachea, curves were obtained which gave an index of the distensibility of the lung

Known volumes of heparinized blood were injected into the pulmonary artery while the pul-

<sup>1</sup> Martin B Macht, *Proc Am Fed Biol Soc* 1943, 3 133



monary veins were occluded and the lung distensibility again determined. The congestion of the pulmonary vessels resulted in a diminished distensibility of the lung. The reduced distensibility was not due to pulmonary edema since the distensibility returned to its previous level after removal of the blood from the pulmonary vessels.

Similar lung distensibility studies were made in living, curarized, open chested dogs. Congestion produced by compression of the pulmonary veins or aorta resulted in diminished distensibility of the lung. Release of the compression resulted in a quick return to the former level of distensibility. Improvement in distensibility resulted from compression of the venae cavae, pulmonary artery or from peripheral circulatory failure.

**Terminal changes in cardiac activity and in respiration in death from severe hypothermia**  
 GEO L MAISON and HANS O HATERIUS *Depts of Physiology and Pharmacology, Boston Univ Medical School*. Under urethane or morphine-urethane anesthesia, and in water between 20 and 5°C, the dog lost body heat at such a rate that his rectal temperature fell approximately 10°C per hour of exposure. This rate of fall did not seem to be influenced by the presence or absence of shivering. Blood pressure and heart rate fell linearly with rectal temperature until a level ca 28°C, at which point the blood pressure tended to follow a plateau at levels between 60 and 80 mm Hg mean pressure, and the heart rate became variable.

The rectal temperature at death varied between 18° and 26.5°C. Three types of electrocardiographic response to hypothermia occurred. In one ventricular fibrillation supervened, with respiration continuing after the last effective cardiac activity. In a second pattern sinus rhythm continued until death, which occurred in cardiac stand-still. In this circumstance, respiration as a rule continued after cardiac standstill had occurred. In the third pattern, auricular standstill was seen and the ventricle continued to beat at rates as low as 3 to 6 per minute for a variable period, in this category death apparently resulted from respiratory failure.

When the cardiac rate fell below 20 the mean blood pressure between beats ranged from 20 to 40 mm Hg, rising to as much as 100 following the forcible systole. Such beats resembled those seen in 'vagal escape'. However, atropinized or vagotomized dogs revealed no effective increase in the survival time. Hematocrit levels are not obviously influenced in rapid death from hypothermia. [*This work was supported in part by Contract W 33 038 ac 14757 with the Aeromedical Lab, Air Materiel Command, A 4 F, Wright Field, Dayton, Ohio*].

**The effect of interpleural adhesions on pulmonary expansion and venous pressure** N S R

MALUF *Laby of Experimental Surgery, Harvard Medical School, Boston*. Adhesions were produced by blowing asbestos powder into the pleural cavities of dogs and withdrawing the air upon closure.

An intratracheal tube with inflatable cuff was used in the measurement of maximal pulmonary expansion and tidal volume and in the production of minimal intrathoracic pressures. Maximal pulmonary expansion was obtained by clamping the outlet and measuring the total volume of air that could be inhaled.

Intrathoracic and intra-abdominal venous pressures were measured in intact animals by radiopaque 10Fr ureteral catheters. Minimal intrathoracic venous pressures were obtained by clamping the inflow respiratory tube. Measurements were made on the same dogs before and three or more weeks after surgery.

1 Interpleural adhesions can cause a diminution in maximal pulmonary expansion even when there is no atelectasis.

2 Atelectasis of an entire lobe does not cause a corresponding decrease in maximal pulmonary expansion.

3 Interpleural adhesions elevate minimal intrathoracic venous pressures only when the central veins are so distorted that they cannot expand normally.

4 Interpleural adhesions do not diminish the effective venous pressure.

5 The pressure in the thoracic inferior vena cava is much lower in the inclined head-up position than in the supine. The probable reasons are (a) the venous return is markedly diminished in the head-up position and (b) the capacity of the thoracic and inferior vena cava is increased by the pull of the abdominal viscera on the diaphragm.

6 In certain instances, the pressure in the abdominal inferior vena cava and external iliac veins rose in inspiration and fell with expiration. On cutting both phrenic nerves in the neck, these pressure relations with the respiratory cycle were promptly reversed.

**A method for the measurement of velocity and volume-flow of blood in the inferior vena cava of intact dogs** N S R MALUF *Laby of Experimental Surgery, Harvard Medical School, Boston*. The purpose of this investigation is to apply the Pitot-static principle to the measurement of the velocity and volume-flow of blood in the inferior vena cava of intact animals. So far as known, this has never been done before in intact animals nor even merely with intact internal veins.

A pair of 10Fr radiopaque ureteral catheters are connected by pressure-tubing to a differential manometer containing trichlorethylene. The tips of the catheters have been cut off transversely to the long axis and slightly tapered. The system is filled with 2% sodium citrate from a Marriotte

bottle and freed from air. The catheters are filled with the citrate, containing 10 units of heparin/cm<sup>3</sup>, through a metal 3-way stopcock by a syringe.

One of the catheters is passed up the inferior vena cava via the femoral, the other catheter is passed down the inferior vena via an antecubital vein or external jugular.

A specially designed commutating stopcock transferred the connections to the opposite limbs of the manometer and thus eliminated possibility of artefact.

Using a model, it was found that the difference in height between the menisci of the manometer is practically a rectilinear function of the volume-flow.

Hyperventilation, in the supine position, did not augment the volumetric rate of flow in the inferior vena cava of the quiet dog.

The Reynolds number was below the critical value, which indicates that the flow was laminar.

**Water intake and membrane hardening of fish eggs.** J F MANERI, K C FISHER and E MOORE (by invitation). *Depts of Biochemistry and Zoology, Univ of Toronto, Toronto, Canada*. Fish eggs, when first shed from the oviduct of the female, appear to be soft, easily deformed globules of yolk. If shed in lake water they increase in size and become round and quite resistant to breakage.

The increase in size, which is due to water entrance into the newly formed perivitelline space, occurs during the first thirty to forty-five minutes after shedding, the eggs of speckled trout often attain a final size of about one-third of the original volume. That the osmotic pressure gradient across the egg membrane is, at least, partly responsible for the water intake is indicated by the absence of swelling in salt solutions isosmotic with the contents of the egg.

The hardening of the outer membrane, or chorion, occur in about two hours after shedding and is dependent upon the previous entrance of water. In lake water the hardness of trout eggs, measured by the weight required to break the egg, reached values 100 times that of oviduct eggs. It has been clearly shown that calcium ions are essential for the process of hardening to occur. In distilled water the eggs are quite soft, if calcium is added they become hard. This hardening in distilled water with added calcium is prevented by the presence of citrate.

**Effect of cerebral concussion upon chemically induced convulsions.** M MARAS (by invitation), M SPIEGEL-ADOLF (by invitation), and E A SPIEGEL. *Depts of Exp Neurology and Colloid Chemistry, Temple Univ, Medical School, Philadelphia, Pa*. The immediate effect of concussion upon the convulsive reactivity was studied in rats, in which convulsions were produced by injection of metrazol (15 mg/100 gram body weight),

and a blow was applied by a pendulum to the freely swinging animal. Immediately following the blow the convulsions usually ceased for about 30-60 seconds. Occasionally a tremor or twitching of the muscles continued for a few seconds before the jerking stopped completely. After a pause of  $\frac{1}{2}$ -1 minute, single contractions or a group of contractions reappeared. While the frequency of the convulsions before the blow as recorded mechanically was about 135 per minute, in the first minutes following the blow it was approximately 25-40 per minute. The experiments indicate that immediately following the blow the reactivity of the brain to the circulating toxin resulting in clonic muscular contractions is transiently depressed or abolished. Then it returns gradually but is quantitatively reduced for several minutes after the blow. Release of acetylcholine from the injured nerve cells does not seem responsible for this post-concussive depression of the convulsive reactivity, since subcutaneous injection of atropine sulfate (1 mg/kilo body weight) which is able to abolish the characteristic abnormalities of the electroencephalogram following a blow (Bornstein) failed to prevent the postconcussive decrease of convulsive reactivity. [Aided by a grant from the John and Mary R Markle Foundation.]

**Electrical control of growth polarity in regenerating *Dugesia tigrina*.** GORDON MARSH and HAROLD W BEAMS (by invitation). *Zoological Labys, State Univ of Iowa*. Cut pieces of *Dugesia tigrina* of known original polarity, one to ten millimeters "relaxed length," were imbedded in 3% agar and exposed to direct current at room temperature for (usually) five days. Aerated 1/20, Ringer's solution in tap water flowed through the wedge trough to provide oxygen and eliminate electrode products.

Pieces oriented with anterior end to cathode regenerated normally at all current densities. Pieces oriented anterior end to anode (a) at or below 5  $\mu$  a/mm<sup>2</sup> regenerated normally, (b) between 6 and 14 showed increasing head behavior in cathode end (tail), becoming subsequently normal, (c) at 15-17 developed head structures and functions in cathode end with subsequent reversion to normal polarity, (d) at 18 became permanently two headed with locomotor competition, common intestine and pharynx usually at right angles to axis, (e) at 19 became bipolar with subsequent suppression of anode head, (f) at 20 and above underwent complete reversal of polarity with head behavior frequently persisting temporarily in tail (original anterior end). Current densities are approximate averages. Length of piece and original body position were not related to effect of current. The potential gradient at reversing strength was about 200 millivolts/millimeter. No "growth inhibition" was found at densi-

ties up to  $31 \mu\text{a}/\text{mm}^2$  Mortality was high, due principally to motor activity of pieces preventing healing, opening lesions and, possibly, anoxia

**Nucleoproteins of rat liver nuclei** ALFRED MARSHAK *Tuberculosis Control Division, U S Public Health Service* Rats were given  $\text{P}^{32}$  as  $\text{Na}_2\text{HPO}_4$  intravenously and three hours later nuclei were isolated using a 5% citric acid and later washed with cold 0.06 M  $\text{MgSO}_4$  in 14 NaCl. On standing in the cold in either the citric acid or the  $\text{MgSO}_4$ -NaCl solutions, only insignificant amounts of  $\text{P}^{31}$ ,  $\text{P}^{32}$ , and purine appear in the solution. The washed nuclei were incubated at  $37^\circ\text{C}$  with desoxyribonuclease until no color could be observed with the Feulgen reaction and with ribonuclease until nucleoli showed little or no color with methylene blue. Controls were incubated with no added enzyme. In all cases  $\text{P}^{31}$  and purine plus pyrimidine appeared in the supernates in approximately the same proportion, indicating that the substrate was nucleic acid in all cases. The specific activity of the  $\text{P}^{32}$  in the supernate was 5 to 6 times as great after incubation with either ribonuclease or with no added enzyme as with desoxyribonuclease. Both in regenerating liver and in normal liver the  $\text{P}^{32}$  appears as nucleoprotein which contains little or no desoxyribonucleic acid.

Data obtained by alternate digestion with ribonuclease and desoxyribonuclease suggest that the substrate although nucleic acid, differs from ribonucleic acid as well as desoxyribonucleic acid. Further experiments are in progress to determine this point. The results also indicate that in the mitotic nucleus desoxyribonucleic acid receives its phosphorus from this as yet unidentified nucleic acid while in the non-mitotic nucleus the phosphorus is transferred to the cytoplasm.

**The blood volume of some elasmobranchs** ARTHUR W MARTIN *Dept of Physiology and Biophysics and Oceanographic Labys, Univ of Washington, Seattle* Previous determinations of the blood volume of fish employed Welcker's method. The dilution method with vital red dye was used in these observations. The fish were restrained out of water but with a stream of sea water passing over the gills. Dye solution was injected into the lumen of the exposed ventricle. Dilution was determined with a Duboseq visual colorimeter after ten to thirty minutes. The specific gravity of fish blood was assumed to be 1.05 in the following computations.

Species	Blood as % of Body Weight
<i>Raja rhina</i> or <i>binoculata</i> (8)	0.8-2.0 Ave 1.5%
<i>Squalus suckleyi</i> (6♂)	3.9-5.9 " 5.2%
" (4♀ without young)	3.9-5.1 " 4.4%
" (4♀ with young)	10.7-13.0 " 11.2%

Fry (Quart J Exper Physiol 7 185, 1914) found that the blood volume in frogs and lizards was not directly related to weight or to surface area. The wide range in weight (7-88 kilograms) is favorable for determining the relation of blood and body weight, and the data for the skate shows that the best relationship is given by the  $\frac{2}{3}$  power of the body weight.

The value for the normal dogfish is slightly higher than that obtained by Derrickson and Amberson (Biol Bull 67 329, 1934) using Welcker's method. Consistent with the striking vascularization of the uterine lining the blood volume of the dogfish carrying young is approximately doubled, even if the weight of the young is included in the computation.

**Arterial pressure gradients, arterial oscillography and cutaneous blood flow in the analysis of arterial obstruction** R T MARTIN (by invitation), A B HERTZMAN and W C RANDALL *From the Depts of Medicine and Physiology, St Louis Univ School of Medicine, St Louis, Mo* The site of the main resistance and of secondary resistances to blood flow in many cases of arterial obstruction may be estimated from arterial oscillography, measurements of arterial pressure gradients and of cutaneous blood flows.

**Methods** The gradients in systolic and diastolic pressures were estimated by an indirect cuff method employing a specially designed oscillograph with photoelectric amplification of the oscillations ("oscillographic index") and detection of the pulses distal to the cuff. The method is sufficiently sensitive to be applicable in the absence of palpable pulses. Cutaneous blood flows were estimated by calorimetric and photoelectric methods.

**Illustrative application in a patient exhibiting Raynaud's phenomenon** During thermal reflex dilatation: pad flows, third finger, indeterminate; index finger, 0.05; fourth finger, 0.09 cc/cm<sup>2</sup>/min (about  $\frac{1}{3}$  of normal). Oscillographic index considerably reduced at wrist and greatly reduced in finger; brachial pressure 100/65; wrist 110/70; digital 75/50. Allen's test for ulnar occlusion was positive. Block of stellate ganglion: pad flow (fourth finger) increased to  $\frac{1}{2}$  of normal; forearm skin flow to  $\frac{1}{2}$  of maximal flow during local mecholyl dilatation; diminished but not absent sudomotor and vasomotor reflexes; arteriogram showed complete block of ulnar artery at wrist and of superficial volar arch; small thin tortuous digital arteries. Conclusion: Main resistance to flow was located in minute arteries of finger skin; secondary and possibly limiting resistance in digital arteries. [Aided by a grant from the United States Public Health Service.]

**The process of feeding in Paramecium** S O

MAST<sup>1</sup> *Biological Laby, Johns Hopkins Univ*  
*Paramecium* contains a shallow ciliated groove, a ciliated tube which leads into the body, and a bundle of fibers (esophageal fibers) which extend posteriorly from this tube. The tube is composed of an outer part (the vestibulum) and an inner part (the pharynx).

The cilia in the pharynx force fluid with particles in suspension against the membrane over the distal opening of the pharynx, producing a sac, the esophageal sac.

More digestible than indigestible particles are ingested. Selection takes place in the vestibulum and the proximal end of the pharynx.

As the esophageal sac enlarges, the particles in suspension in it become concentrated, owing to the passage of water through the membrane into the cytoplasm. A portion of this sac is constricted off, as a food-vacuole, probably by the esophageal fibers. The initiation of this constriction is probably due to periodicity in the action of the fibers, the size of the sac, and the composition of its contents.

The food vacuoles vary greatly in size and frequency. The size is correlated with the quantity and the quality of particles in the surrounding fluid, the chemical composition of this fluid, the rate of ingestion, the rate of loss of water from the esophageal sac, and the length of the intervals between successive constrictions of the esophageal fibers, the frequency is correlated with the quantity and the quality of particles in the surrounding fluid and the acidity and the temperature of this fluid.

Changes in the food-vacuole and digestion in *Paramecium*. S. O. MAST<sup>1</sup> *Biological Laby, Johns Hopkins Univ*. On its course through the body, the food-vacuole first decreases slowly in size, and the acidity of its content simultaneously increases, then it enlarges very rapidly and the acidity decreases. The extent of these changes varies enormously. Acidity in some vacuoles increases to pH 1.4 or more and then decreases approximately to pH 7.8.

The changes in size are due to difference between internal and external osmotic concentrations and to the action of the stretched vacuolar membrane. The increase in acidity is probably due to loss of water, to secretion of acid by the cytoplasm adjoining the vestibulum and the pharynx and to impermeability of the vacuolar membrane to hydrogen-ions. The decrease in acidity is due to entrance of alkaline fluid from the cytoplasm.

The increase in acidity probably causes hydrolysis and thereby an increase in osmotic concentration which results in inflow of fluid containing digestive enzymes.

Death of ingested living organisms is probably largely due to toxic substance produced by the pharynx and concentrated in the food vacuole. Concentration is presumably due to impermeability of the vacuolar membrane to the toxic substance and to loss of water.

*Paramecia* digest protein, fat, and starch. Digestion occurs during the alkaline phase of the food-vacuole. The enzymes involved originate in the ingested organisms and also in the cytoplasm, from which they are carried into the food-vacuole by the cytoplasmic fluid which enters during the rapid enlargement.

The neutral-red granules and the mitochondria are probably not involved in digestion.

Electrical phenomena in mammalian smooth muscle. WALTER J. MEEK, J. A. E. EISTER, J. W. SUTZMAN and W. E. GILSON (by invitation). *Dept. of Physiology, Univ. of Wisconsin, Madison*. The retractor penis muscles of the dog was studied by means of unipolar differential non-polarizable electrodes and delicate electromyographs. Recordings were made with a three channel cathode ray oscillograph. Brief tetanic stimulation of the sympathetic chain below the fifth lumbar resulted in contraction and electrical oscillations from all parts of the muscle as shown by the differential leads. Usually electrical oscillations appeared simultaneously at the distal and proximal ends of the muscle. Following this each end developed a series of waves or a series of groups which were independent of each other. A comparison of unipolar and differential curves taken simultaneously seems to show that at first there is a movement of charges in the field but shortly thereafter discharges are made from localized areas without field movements. Contractions as shown by the myographs agreed on the whole with the potential changes. Contractions usually occurred nearly simultaneously at each end of the muscle but either end might on occasion precede the other, or one end might contract without the other. Direct stimulation of the muscle gave responses which were not essentially different from those obtained by nerve stimulation.

The results seem in agreement with the idea that the retractor penis muscle belongs to the multiunit type of smooth muscle described by Bozler in which nerve fibers activate many units. The initial distribution of excitation on nerve stimulation is therefore somewhat like that in skeletal muscle. The sustained contractions however are accompanied by a long series of electrical oscillations which may originate from more than one focus.

Substances in blood of patients during emotional states. Effect on the isolated rabbit intestine. A. T. MILHORAT and O. DIETHELM (by invitation). *Depts. of Psychiatry and Medicine*

<sup>1</sup> Deceased

*Cornell Univ Medical College, The Russell Sage Inst of Pathology and The New York Hospital, New York.* Investigations previously reported by us showed that the blood of patients during certain emotional states contain substances that have effects on the contraction and relaxation of the isolated intestine of the rabbit. Samples of blood withdrawn when the predominating emotion was anxiety had effects resembling those of epinephrin, while blood taken during states of emotional tension induced changes similar to those seen after addition of acetylcholine. In the many instances in which anxiety and tension existed together, both types of effects were observed. When the effects of acetylcholine were prevented by previous treatment of the intestine with hyoseyamine, the cholinergic effects of the blood samples were similarly prevented, suggesting that the substance in the blood having these effects probably is acetylcholine. Under these circumstances, the adrenergic effect when present often was increased. Dibenzamine, in the amounts used, reduced but did not prevent the effects of both epinephrin and the adrenergic substances in the blood. The blood of some patients induced increased amplitude of contractions and shortening of the intestine after the preparation had been treated with hyoseyamine, these effects were absent in the untreated intestine. There appears to be a relationship between these effects and the presence of resentment as the predominating emotion.

**The excretion of the blue dye T-1824 in the bile.** A. T. MILLER, JR. *Dept of Physiology, Univ of North Carolina Medical School, Chapel Hill.* The hepatic removal of intravenously injected T-1824 has been studied because of its bearing on the interpretation of the T-1824 disappearance curve. Spectrophotometric analyses of hepatic bile and of blood serum, supplemented by chemical separation of the dye from bile, permitted the following conclusions:

- (1) Very little dye appears in hepatic bile in the first 30 minutes after injection.
- (2) Maximum dye concentration in bile is reached 60 to 90 minutes after injection, dye concentration then declines slowly, paralleling the fall in plasma dye concentration.
- (3) Dye concentration in the bile is always lower than (usually less than one-half) the simultaneous plasma dye concentration, but roughly proportional to it.
- (4) The equilibrium dye concentration in bile is not due to the saturation of a secretory mechanism (as in renal Tm) because a second injection of dye results in a second rise in dye concentration in bile.
- (5) The concentration of dye in bile bears no obvious relation to the rate of bile flow

within the limits of flow rate encountered (2 to 10 ml of bile per hour).

- (6) The excretion of dye in the bile in the first 2 to 5 hours following injection accounts for only 2 to 5 per cent of the dye which leaves the bloodstream in that interval. Hence liver function is presumably not a limiting factor in the rate of dye disappearance.
- (7) The concentration of dye in bile parallels (but at a lower level) that of dye in thoracic duct lymph.

**The catheptic activity of tissues of normal and alloxanized rats.** I. ARTHUR MIRSKY and R. H. BROTH-KAHN (by invitation). *May Inst for Medical Research of the Jewish Hospital, Cincinnati, Ohio.* Tissue extracts of the leg muscles and livers of normal and alloxanized rats were prepared by blending the respective tissues in cold citrate buffer at pH 3.5. The catheptic activity of these extracts was then determined by the method of Anson by measuring the amount of tyrosine liberated during their incubation with a denatured hemoglobin substrate at pH 3.5.

In both normal and alloxanized rats, the liver extracts were significantly more active than the muscle extracts. The results indicated that such extracts of the livers of alloxanized rats show a definite increase in catheptic activity as compared to similar extracts from non-alloxanized rats. On the other hand, extracts of the muscles of normal and alloxanized rats did not differ appreciably in their activity.

The direct addition of insulin to the liver extracts from alloxanized rats or the injection of insulin into alloxanized rats three hours pre-mortem did not lower the activity of these extracts to the range of values observed in liver extracts from normal animals.

**Histochemical analysis of the sebaceous glands of the hamster.** WILLIAM MONTAGNA (by invitation) and JAMES B. HAMILTON. *Dept of Anatomy, Long Island College of Medicine, Brooklyn, New York.* The two dorsal melanotic spots of the hamster are sites of large, densely-packed sebaceous glands. Histochemical studies of these glands in normal males show the following:

**Lipids.** (a) Sebum and the large central cells in sebaceous alveoli, but not the small peripheral cells, stain intensely with Sudan IV. (b) Sudan black-B stains the whole gland, including the peripheral cells, although the latter react less. (c) With the Smith-Dietrich method it appears that the peripheral zone and sebum contain phospholipins. (d) Nile blue sulphate, which stains unsaturated triglycerides a rose color, reveals them primarily in the sebum, in cells undergoing sebaceous degeneration, and in mature sebaceous cells. Triglycerides are absent in the peripheral zone and in diminished amounts nearby. (e) Sebum has

birefringent lipid crystals which dissolve in acetone and other solvents, and do not form digitonides (f) The Feulgen reagents and 2-4 dinitrophenylhydrazine, which demonstrate "plasmalogens," stain sebum with moderate intensity, acinar cells very weakly

**Enzymes** (a) Minute quantities of alkaline phosphatase are present diffusely throughout the gland and sebum Occasionally the enzyme is more abundant along the periphery of the gland (b) Acid phosphatase exists in appreciable amounts in sebum and the entire gland The quantities are small only at the periphery of the glands, and in cells undergoing sebaceous degeneration (c) Lipase activity is strong only in the sebum and cells undergoing sebaceous breakdown, it is absent in peripheral cells (d) Application of the M-Nadi reagents reveal only traces of "stable" cytochrome oxidase in glandular cells and sebum

An experimental study of intramuscular pressure measurements CAMPBELL MOSES (introduced by C C Guthrie) *Dept of Physiology and Pharmacology, School of Medicine, Univ of Pittsburgh* In this study an attempt was made to analyze the reliability and significance of intramuscular pressure determinations After trial of Kerr and Scott's modification of Henderson's method (*Adventures in Respiration*, pg 243) of measuring intramuscular pressure and of Gunther's method (*J Lab Clin Med* 27 1939, 1942), the former was adopted In rabbits the effect on intramuscular pressure of (a) sciatic stimulation, (b) occlusion of the abdominal aorta and/or vena cava, (c) spinal cord section, (d) hemorrhage, (e) curarization, and (f) coramine administration were studied In man simultaneous observations of blood pressure, venous pressure and intramuscular pressure were made before, during, and after surgical procedures performed under spinal anesthesia

In rabbits the intramuscular pressure determinations showed little change with these procedures or after death In human muscles with dense sheaths such as the extensors of the wrist and of the knee, voluntary contraction or local venous obstruction increased the intramuscular pressure After spinal anesthesia no change was found in the intramuscular pressure in human gastrocnemius or biceps In 14 surgical patients no correlation was observed between the intramuscular pressure and either the venous pressure or the arterial blood pressure

Diurnal variation in the specific gravity of the blood, serum, corpuscles, and hematocrit reading CAMPBELL MOSES (introduced by C C Guthrie) *Dept of Physiology and Pharmacology, School of Medicine, Univ of Pittsburgh* The diurnal variation in the specific gravity of the blood and serum and in the hematocrit reading were de-

termined in 10 patients on a standard hospital routine Withholding food and fluids for 12 to 18 hours was followed in some instances by an increase in the specific gravity of the blood and serum and in the corpuscular hematocrit reading, but this was not a constant finding The specific gravity of the corpuscles calculated from the specific gravity of the blood and serum and the hematocrit was also found to undergo considerable diurnal variation In these hospitalized patients there was no time during the day when consistently higher or lower readings were obtained, and, therefore, an optimum time for sampling was not indicated

**Role of the nervous system in early and late hypertension in the dog** W G MOSS (by invitation) and G E WAKERLIN *Dept of Physiology, Univ of Illinois College of Medicine, Chicago* Ogden and co workers have reported that the nervous system takes over the maintenance of late hypertension in the rat in contrast to early hypertension which is maintained by a humoral mechanism We have studied this problem in relation to early and late renal hypertension in the dog and have included parallel observations on neurogenic hypertensive dogs

Ether, pentothal sodium, pentobarbital sodium, morphine plus pentobarbital sodium, and epidural procaine were used in anesthetic doses There was no consistent difference in the effects on the blood pressures of early and late renal hypertensive dogs Reductions in blood pressure were greatest in neurogenic hypertensive animals

An adaptation of the "cold pressor" test was applied to these three groups of dogs The average response in the various groups was essentially the same

Several autonomic blocking drugs (dihydroxyergotamine, 2 benzyl-4,5 imidazoline [Priscol], dibenzyl  $\beta$ -chloroethyl amine [Dibenzamine], atropine, and tetraethylammonium chloride) were used to analyze vasomotor activity in the three groups of dogs The blood pressure responses to these drugs showed certain differences which will be discussed

The foregoing evidence, still incomplete, suggests the possibility of a definite role for the nervous system in the maintenance of late renal hypertension in the dog As reported by others, the nervous system was found to play a major role in the maintenance of neurogenic hypertension [*This work was aided by a grant from the John and Mary R Markle Foundation*]

**Influence of intermittent positive pressure breathing on cardiac output** HURLEY L MOTLEY (by invitation), LARS WERKO (by invitation) and ANDRE COURNARD *Dept of Medicine, College of Physicians and Surgeons, Columbia Univ, NYC* Intermittent positive pressure breathing (IPP) was studied in 20 human subjects with essentially

normal circulation. The pressure was increased in the thorax during inspiration by means of automatic respirators producing different kinds of mask pressure curves. Cardiac output was determined by the direct Fick method (Cournaud, Federation Proceedings 4: 207, 1945) with the subject supine and in a fasting state. Control cardiac outputs were determined at ambient pressure before and after the IPP. Simultaneous pressure tracings were recorded from the right heart, peripheral artery and face mask. Mean mask pressure was determined by planimetric integration. Three types of IPP mask curves were compared: (I) symmetrical with gradual increasing and decreasing slope, expiratory time approximately the same as inspiratory and minimal expiratory pressure above atmospheric, (II) asymmetrical with rapidly increasing pressure during inspiration and rapidly dropping during expiration, long inspiratory and short expiratory time intervals and minimal expiratory pressure above atmospheric, and (III) asymmetrical with gradually increasing pressure during inspiration and suddenly dropping early in expiration to atmospheric and expiratory time equal to or exceeding inspiratory. The results obtained are summarized in the table.

Type of Mask Pressure Curve	I	II	III
Number of Experiments	16	10	7
Mean Mask Pressure mm Hg	7.0	10.6	5.7
Per cent Change in Cardiac Output	-14.5	-16.5	+6.0

Correlation between height of mean mask pressure and decrease in cardiac output was good in I and II, but did not apply to III, as no decrease occurred in any case. [Aided by contract with Aero-Medical Lab., Wright Field, and grant from the Commonwealth Fund.]

The effect of fatigue on the solubility of myosin. R. G. MRAZEK, JR. (by invitation) and C. I. REED, Dept. of Physiology, Univ. of Illinois, Chicago College. Deuticke reported that the degree of fatigue of skeletal muscle proportionately decreased the solubility of myosin. Experiments on frog gastrocnemii *in situ* showed a nitrogen yield from controls of 1.20 grams %, 0.98 grams % from fatigued muscles,  $T = 2.48$  which represents a significant difference. A similar experiment on rat gastrocnemii yielded 1.69 grams % in the fatigued group,  $T = 1.099$ , statistically insignificant. In another group of rats, the gastrocnemius was tetanized for 1 minute after complete fatigue with single shocks then processed. The control muscles yielded 1.36 grams % of N, the fatigued muscles 1.18 grams %,  $T = 3.85$  a highly significant factor. In a similar group of rats, unfatigued muscles tetanized in an identical manner showed significant differences between control and fatigued muscles. Evidently the duration of

activity before the state of fatigue is reached is an important factor. The Deuticke effect is demonstrable only after alkaline extraction. Deficiency of vitamin B-complex resulted in a greater yield of N from both muscles, but there was no significant difference between the control and fatigued muscles.

The preparation of prothrombin by adsorption on, and elution from aluminum hydroxide. F. L. MUNRO and MURIEL PLATT MUNRO (introduced by J. E. Thomas), *Charlotte Drale Cardeza Foundation, Dept. of Medicine, Jefferson Medical College and Hospital, Philadelphia*. Partially purified prothrombin can be prepared by direct adsorption from plasma with aluminum hydroxide gel followed by elution with phosphate buffer.

Adjust oxalated plasma to pH 8.0, add 4% of its volume of aluminum hydroxide gel, mix, and allow to stand for 15 minutes. Centrifuge, suspend the aluminum hydroxide in 0.15 *N* sodium chloride containing 0.92 grams potassium oxalate per liter, and recentrifuge. Elute the prothrombin from the aluminum hydroxide with 0.2 *M* phosphate buffer pH 8.0, using a volume equal to that of the plasma. Remove the suspended aluminum hydroxide by centrifuging, adjust the supernatant to pH 7.4-7.6, and dialyze to remove the phosphate. All procedures are carried out in the cold.

By this procedure 50% or more of the prothrombin in the plasma may be obtained in a solution containing 7-8 mg of nitrogen per 100 ml. The prothrombin is stable for several days at 5°C and spontaneous conversion to thrombin is slow. Conversion to thrombin in the presence of thromboplastin and calcium ions is complete within one minute and no evidence has been found of the presence of antithrombin.

Changes in blood lymphocytes in normal and resistant rats following traumatic shock. D. D. MUNRO (by invitation) and R. L. NOBLE, *Research Inst. of Endocrinology, McGill Univ.* It has been found that when normal rats are traumatized in the Noble-Collip drum that a marked fall in the relative and absolute number of circulating lymphocytes occurs, the extent of the decrease being directly related to the amount of trauma. A return to normal levels takes place within forty-eight hours, recovery being more rapid with the smaller amounts of trauma. When rats are exposed to amounts of trauma producing mortality the most rapid and severe lympholysis occurs in those rats which eventually die.

In a comparison of trauma resistant rats with normals a strikingly different behavior of the lymphocytes is apparent. The initial blood level of lymphocytes is higher, the fall in circulating lymphocytes after trauma is markedly less and recovery to normal levels is more rapid in resistant rats. The degree of resistance can apparently





pressure changes and certain evidence from kidney volume changes suggest that the pressure increases were the result of peripheral vasomotor changes.

**Effect of hemorrhage on intestinal absorption of chloride in the presence of sulphate** DAVID W. NORTHUP, J. CLIFFORD STICKNEY, and EDWARD J. VAN LIERE. *Dept of Physiology, School of Medicine, West Virginia Univ., Morgantown.* The absorption of chloride, sulphate, and fluid from a mixture of equal parts of isotonic NaCl and isotonic Na<sub>2</sub>SO<sub>4</sub> placed in Moreau loops of the lower intestine of barbiturized dogs for 40 minutes was studied. Half of the dogs had been bled 3% of their body weight under light ether anesthesia four hours previously, the controls were subjected to a dummy operation at the same time.

The per cent absorption in control and experimental dogs respectively was 69 and 80 of the chloride, 24 and 30 of the sulphate, and 34 and 45 of the fluid. None of these differences was statistically significant.

The final chloride concentration was 0.187% in the control and 0.138% in the experimental dogs (chloride as NaCl). This difference was not significant. The final sulphate concentrations showed little difference: 1.17% and 1.22% (as Na<sub>2</sub>SO<sub>4</sub>).

**Micro-colorimetric determination of urinary estrogens over short periods of time** M. JANE OESTERLING (by invitation) and WILLIAM T. SALTER. *Laby of Pharmacology and Toxicology, Yale Univ. School of Medicine, New Haven, Connecticut.* By treating partially purified extracts of urine with the Kober reagent (phenol-sulfonic acid) and then separating out the colored component on the basis of differential solubility in solvents of varying polarity, it is possible to achieve a satisfactory purity of color. A final correction by means of optical densities must be made for a brown colored impurity. This correction involves the use of arbitrary constants, and the error may be great if the impurity cannot be reduced to a minimum by preliminary purification. The procedure is applicable to one-fourth of a day's urine. The urinary estrogen of normal adult males by this method is about ten micrograms per twenty-four hours. Females near menstruation, show somewhat higher values which rise at ovulation to values of 70 or more micrograms per twenty-four hours. High values are recorded by this method in abnormal situations like male homosexuality, prostatic disease, and in certain hermaphrodites. Perhaps such abnormal chromogenic compounds are not true estrogens. Nevertheless, the test is useful as a screening method because it separates low estrogenic concentrations from the possibly high ones and may be applied to monkeys and man over intervals of a few hours. Early in pregnancy the values rise to nearly a thousand micrograms per twenty-four hours. The major

part of this material is in the form of estriol rather than in the combined estradiol-estrone fraction. [Work aided by grants from the National Cancer Institute Act, Navy contract N6ori 44, Task Order #VI, and the Donner Foundation.]

**Total body water as related to urea elimination** ERIC OGDEN. *Dept of Physiology, Univ of Texas School of Medicine, Galveston.* Marshall demonstrated that urea is uniformly and rapidly distributed in body water. Diuresis lowers the plasma urea content in dogs enough to make computation of the total body water feasible by considering the excess urea eliminated and the change in plasma urea concentration during the period of diuresis according to the following equation:

$$W = \frac{[(UV)_0 - (UV)_1]T}{(P_1 - P_2)10}$$

- where W = Total body water (liters)  
 P<sub>1</sub> = Concentration of urea in plasma water before diuresis (mg/100 cc)  
 P<sub>2</sub> = Concentration of urea in plasma water at end of diuresis (mg/100 cc)  
 (UV)<sub>1</sub> = Urea output into bladder per minute before diuresis (mg/minute)  
 (UV) = Urea output into bladder per minute during whole period of diuresis (mg/minute)  
 T = Total duration of diuresis (minutes)

Administration of water produces a moderate lowering of urea with a new equilibrium level in about two hours. Intravenous glucose may produce a more marked lowering of plasma urea in about one and one-half hours.

Dehydration must not be violent enough to stimulate urea formation since the assumption must be made that the rate of urea production has not changed during the procedure. Due allowance must be made for the water intake and output during the period of the experiment. Other possible sources of error are under investigation.

**Treatment of experimental renal hypertension with paredrine hydrobromide** E. A. OHLER (by invitation) and G. E. WAKERLIN. *Dept of Physiology, Univ of Illinois, College of Medicine, Chicago.* In view of the possibility that experimental renal hypertension may involve increased formation of pressor amines by the kidney and that the administration of a pressor amine may enhance the enzymatic destruction of such pressor amines, we administered p-hydroxy-methyl-phenethylamine (Paredrine HBr) in a dosage of 0.01 mg/kg intramuscularly daily to four chronic renal hypertensive dogs for a period of two weeks. Approximately this dosage has previously been re-

duction in blood volume was only  $0.7 \pm 1.64$  cc/kg. In no animal was blood volume reduced enough to account for the reduction in bleeding volume. The loss of bleeding volume cannot be attributed to damage done during the first bleeding volume measurement. In a group of thirteen control animals subjected to two bleeding volume determinations at similar time intervals, but with complete re-infusion at the end of the first, the average bleeding volume loss was only  $0.69 \pm 1.54$  cc/kg, with a blood volume reduction of  $3.87 \pm 2.27$  cc/kg.

**Ionic balance and correlated psycho-physiological measurements in premenstrual tensional states.** RICHARD R. OVERMAN, THERON S. HILL (by invitation) and HUDSON JOST (by invitation). *Depts. of Physiology, Neurology and Psychiatry, Univ. of Tennessee, College of Medicine, Memphis*. Serial flame photometric measurements of Na and K and chemical measurements of Cl in blood, plasma, erythrocytes and urine, 24 hour urine volume, fluid intake, hematocrit and vaginal smears were correlated with electroencephalographic, electrocardiographic and Keeler polygraphic recordings taken during the menstrual, follicular, ovulatory and luteal phases of the menstrual cycles of seven patients. Of these, three had no previous or current disorder other than mid-cycle, premenstrual or menstrual syndrome, one had premenstrual tension and epileptic seizures, two had been psychotic previously and one was psychotic when the studies were made.

While the ionic concentrations in whole blood showed no consistent trends, plasma sodium concentrations were uniformly higher in the intermenstrual and early premenstrual periods. During these periods the vaginal smears indicated the highest estrogen levels and water retention occurred. Evidence of cortical cell instability, as detected by the Davis rating, spectrum analysis, and per cent time alpha of the electroencephalograms likewise occurred in the mid-cycle and premenstrual phases.

The Keeler polygraphic records, although as yet lacking standardization with reference to per cent of normal population, revealed an increase in frequency and irregularity of respiratory pattern as the cycle progressed. Likewise, the galvanic skin resistance was more stable during menstruation and became progressively less stable in mid cycle and early premenstruum.

Significant relationships between reactivity of the central and autonomic nervous systems, ionic balance and fluid storage are indicated by these studies. [Research supported by a grant-in-aid from the U. S. Public Health Service.]

**Blood and "extracellular" fluid volumes and ionic balance in human therapeutic malaria.** RICHARD R. OVERMAN, A. K. DAVIS (by invita-

tion) and ELVA THARP (by invitation). *Dept. of Physiology, Univ. of Tennessee College of Medicine, Memphis*. Serial determinations of plasma volume, "extracellular" fluid volume and Na, K and Cl concentrations in blood, plasma, red cells and urine have been made on 26 neurosyphilitic patients with therapeutic *P. vivax* or *P. falciparum* infections. Each of the fluid compartment measurements were related to the body weight of the patient at the time of determination.

Feldman and Murphy (*J. Clin. Invest.* 24: 780, 1945) have previously reported that an increase in the total blood volume occurs in early malaria. However, when related to the body weight either an increase or a slight decrease may occur. In late malignant infections (*falciparum*) a reduction in blood volume to lethal levels has been seen in a few patients who, however, responded well to red cell transfusions.

The "extracellular" fluid volume, as measured by the dilution of NaSCN, progressively increases throughout the course of both *vivax* and *falciparum* infections. The apparent "extracellular" fluid volume may become increased to the point of being equal to the calculated total body water. It is apparent that in human malaria as in simian malaria (*J. Lab. and Clin. Med.* 31: 1170, 1946) NaSCN no longer measures the extracellular fluid compartment but enters the cells and is diluted by the total body water (except CSF).

Flame photometric determinations of the native ions Na and K in erythrocytes reveal a similar redistribution in that the Na concentration rises and the K concentration is reduced. [Research supported by a grant from the U. S. Public Health Service.]

**Reversible permeability alterations in the erythrocytes of the malarious monkey.** RICHARD R. OVERMAN. *Dept. of Physiology, Univ. of Tennessee College of Medicine, Memphis*. It has previously been shown that the tissue cells of the monkey fatally infected with *P. knowlesi* become permeable to the foreign ion, SCN. Such altered permeability is reversible following chemotherapeutic intervention (*J. Lab. and Clin. Med.* 31: 1170, 1946). Alterations in the permeability of the erythrocytes to native ions (Na, K, and Cl) have now been observed.

Flame photometric analysis of Na and K in red cells of normal monkeys reveal average Na concentrations of 45 mg per cent (range 27 to 77 mg per cent) and average K concentrations of 447 mg per cent (range 385 to 512 mg per cent). Upon infection with *P. knowlesi* a progressive increase in Na concentration is observed which reaches an average value of 81 mg per cent (range 68 to 106 mg per cent) with a concomitant progressive fall in K concentration to an average of 302 mg per cent (range 183 to 376 mg per cent).

within 24 hours preceding death. Chemical determination of Cl reveals alterations in the distribution of this ion in the same direction as the Na shift and of approximately the same degree. Animals in which the fatal course is averted by chemotherapeutic means show a slow return to normal in the distribution of Na, K, and Cl between red cells and plasma.

It is suggested that redistribution of these ions in malaria (and perhaps other febrile diseases) may be followed by severe metabolic disturbances leading to a fatal outcome. [Research supported by grants from the Office of Scientific Research and Development and the U. S. Public Health Service.]

**Nonspecificity of the patho-physiology of the radiation syndrome.** E. E. PAINTER, C. L. PROSSER and M. N. SWIFT (by invitation). *Argonne National Lab., Chicago, Illinois, Loyola Univ. School of Medicine, Chicago, Illinois and Univ. of Illinois, Urbana, Illinois.* Nearly every organ system is affected by a single 30 day LD<sub>50</sub> dose of any type of ionizing radiation. The most sensitive systems are the blood-forming organs, the gastro-intestinal tract and the gonads. An increased sedimentation rate, delayed clotting time, moderate anemia, increased plasma volume, decrease in fecal and urinary coproporphyrin, increased plasma clearance of phenol red, increased blood sugar and acetone bodies, diminution of plasma NPN, urea N, "polypeptide N," and total proteins, elevated urobilinogen and bilirubin, decreased gastric acidity, and low urine chloride indicate the preterminal changes in other systems. Terminally there are marked changes in the peripheral circulation, the heart, the kidneys and the central nervous system. Some of these radiation effects are direct and some, indirect, as a result of toxic agents or of hypoxia, infections and other secondary factors.

No single chemical reaction is peculiarly specific for irradiation damage. A similar preterminal course with leucopenia and high sensitivity of dividing cells is found with such agents as the nitrogen mustards (Gilman and Philips), the acute terminal course with fever is similar in acute infections and in many diseases. There are striking similarities to anaphylactic shock and to the nonspecific (alarm) reactions to a variety of diverse toxic agents given in sublethal amounts (Selye). Many of the delayed effects of irradiation can be duplicated by various toxic chemicals, e.g., anemia in benzol and phenylhydrazine poisonings, or tumor induction by coal tar derivatives.

Urea secretion of chick mesonephric tubules in tissue culture. GEORGE PALLADE, (Visiting Fellow, Rumanaia) (introduced by Robert Chambers). *Dept. of Biology, Washington Square College, New York Univ., New York.* In cooperation with Dr. Robert Chambers a micromanipulative method

was devised for handling minute quantities of aqueous solutions of known dimensions suspended in a drop of an inert oil in a chamber under the compound microscope. This method was used for testing the presence of urea in the fluid removed with a micropipet from the proximal tubular cysts of 9-14 day embryo chick mesonephros grown for 36 to 48 hours in tissue culture. The determination of urea was based on the ammonia released by adding urease, the developing alkalinity being detected by the pH virage of phenol red. Amounts as small as 0.05 cu mm can be handled and the sensitivity of the method is the order of 0.01-0.005.

No urea could be detected in the tubular cysts until urea, in amounts of 1/10000-1/20000, had been added to the culture medium. A concentration of the urea in the cystic fluid was then found, on the average, to be doubled. A rough evaluation of the difference between urea concentration in the medium and in the cysts was made, after adding urease, by estimating the quantity of NaH<sub>2</sub>PO<sub>4</sub> necessary to bring the pH back to 7. The NaH<sub>2</sub>PO<sub>4</sub> solution is introduced in the drop, in which the urea hydrolysis had been carried, also through micromanipulation.

The urea seems to be concentrated in the cysts through a secretion process, but the concentration rate appears to be low.

**Thermocouples for the measurement of the surface temperature of the skin.** EDWARD D. PALMES and CHARLES R. PARK (introduced by Ray G. Daggs). *Armored Medical Research Lab.* A method of mounting thermocouples was developed to give skin temperature readings comparable to those obtained with a radiometer. A thin, elongated thermal junction was soldered to the undersurface of a small rectangle of 16 mesh copper window screen. The insulated leads passed up through the screen and were lashed with thread to its upper surface. The assembly was held in firm contact with the skin by bands of elastic cloth fastened to each end of the wire screen.

Temperatures taken simultaneously on the same skin area by this thermocouple assembly and by a radiometer showed very small differences between the two methods even when the skin was grossly wet with sweat.

The simplicity, stability of calibration, speed, and ease of conversion of E.M.F. values to temperatures made the measurement of radiant skin temperature much more convenient by this thermocouple than by radiometer.

**An apparatus and method for the continuous measurement of evaporative water loss from human subjects.** EDWARD D. PALMES (introduced by Ray G. Daggs). *Armored Medical Research Lab.* The subject was placed in a chamber through which a steady flow of air at constant temperature

and humidity was maintained by an air conditioning unit. The inlet and outlet air streams of the chamber were analysed for water vapor simultaneously by a special modification of an N D R C Selective Gas Analyser, Model IV. The optical system of the analyser was altered so that one beam of infra-red radiation passed through a sample of inlet air and a parallel beam through a sample of outlet air. The difference in absorption of radiation caused an electrical imbalance in the receiving thermopile, and this was amplified and recorded as a continuous tracing.

From this record it was possible to calculate a virtually instantaneous evaporative rate or total evaporative loss over a period of time by using a factor derived from the rate of air flow and the calibration data for the analyser. Evaporation in experiments lasting several hours was thus computed and the results were checked against evaporative loss determined independently from the weight change of the man.

The apparatus and method were applied to measurement of evaporative loss from normal and febrile subjects, at ambient temperatures from 80° to 110°F. Satisfactory results were obtained during periods of insensible water loss, of high and variable sweat rates, and during violent shaking chills.

**A technic of human calorimetry** EDWARD D. PALMES and CHARLES R. PARK (introduced by Ray G. Daggs) *Armored Medical Research Lab., Ft. Knox, Ky.* The nude subject was enclosed in a small chamber through which a constant flow of air was maintained. The increase in water vapor concentration in the air passing over the man, which was recorded continuously by an infra-red gas analyser, was the measure of evaporation. Metabolism was determined by a closed circuit apparatus which recorded oxygen consumption continuously. Environmental, rectal, and skin temperatures were determined by thermocouples. New mountings were devised for the thermal junctions used on the skin, and true surface temperatures were obtained even in the presence of heavy sweating. Radiation could be computed using the wall and mean skin temperatures, and storage was calculated from the skin and rectal readings. Convection was obtained by algebraic summation of the above values.

Close control of the environment within the test chamber could be obtained, and studies of the heat exchange of normal and febrile subjects were made successfully in ambient temperatures ranging from 80° to 110°F. Pilot studies indicated that the method was well suited to the calorimetry of clothed and working men.

The advantages of this technic were that all heat exchanges could be measured either continuously or at short intervals, rapidly changing and

high rates of evaporation and metabolism were determined without difficulty, and experiments could be carried out for periods as long as eight hours without discomfort to the subject.

**On the distensibility of the arteries** J. R. PAPPENHEIMER *Dept. of Physiology, Harvard Medical School.* The internal cross sectional areas of mammalian arteries were measured at different pressures in isolated segments and in the arteries of anesthetized animals. For in vitro measurements, arterial segments (8 to 15 mm long and 0.65 to 4.7 mm i.d. at 100 mm Hg) were suspended on hollow steel cannulae and perfused with Ringer's solution at known pressures. The outside walls were exposed to mineral oil or to an isotonic glucose drip. The segment formed one arm of a conductivity bridge, the off-balance potential of which was amplified and measured with an oscilloscope. The conductivity determined by balancing the bridge is proportional to the internal cross sectional area after correction (approx. 10 per cent) for the conductivity of the wall. The latter acts as a constant resistance in parallel, the value of which is determined during perfusion with oil or isotonic glucose solution.

In the physiological range of pressures the relative change of area per unit pressure (volume-elasticity) diminishes with the absolute diameter of the artery. The implication of this finding for the relations between pressure and flow of blood in the peripheral circulation will be discussed.

For in vivo measurements the electrodes project from the tips of glass needles inserted into the blood stream through the arterial wall. In this case conductivity is calibrated in terms of the off-balance potential which is rectified and used to drive recording oscillographs. With simultaneous recording of pressures the method may be employed to study the viscous as well as the elastic properties of the arteries.

**Influence of female sex hormone on uptake of radioactive iodine by the thyroid** K. E. PASCHKIS, A. CANTAROW and W. PEACOCK (by invitation) *Jefferson Medical College and Hospital, Philadelphia, Pennsylvania and Dept. of Physics, Massachusetts Inst. of Technology, Cambridge, Massachusetts.* Reports in the literature on the influence of estrogenic hormone on thyroid activity are controversial.

The uptake of iodine by the thyroid is a measure of one phase of thyroid function. This was studied by means of a tracer dose of  $I^{131}$ .

The uptake of iodine by the thyroid of spayed rats did not differ from that of normal controls. Treatment of female rats with estradiol benzoate for periods of one to four weeks failed to influence iodine uptake as compared to that of untreated controls.

It is concluded that the functional capacity of

the thyroid gland for iodine uptake is not influenced by estrogenic hormone

Different periods of administration of enterogastrone and urogastrone in double histamine experiments T L PATTERSON, J KAULBERSZ, D J SANDWEISS and H C SALTZSTEIN (by invitation) *Wayne Univ College of Medicine and Harper Hospital, Detroit, Mich* Although a comparison has been previously made between the physiological action of urogastrone and enterogastrone it seems desirable to take into consideration certain differences depending on what period the injection was made in a double histamine experiment

Enterogastrone was prepared from the intestines of six normal female dogs by the method employed by Greengard The urogastrone was obtained from normal female dogs' urine after the method of Gray et al

Enterogastrone introduced in the first period inhibited the total output of free HCl in 11 out of 12 experiments The inhibition varied between 22 and 89 per cent When administered in the second period it inhibited in 10 out of 12 experiments The inhibition ranged between 14 and 86 per cent

Urogastrone injected in the first period inhibited the total output of free HCl in 21 out of 32 experiments The inhibition fluctuated between 10 and 85 per cent When it was applied in the second period, 10 of 15 experiments produced inhibition ranging between 12 and 70 per cent

The average inhibition of the enterogastrone administered in the first period was much higher, 51 per cent as compared to 25 per cent for the urogastrone Whereas, similar injections introduced in the second period gave nearly the same inhibition (enterogastrone 24 per cent and urogastrone 27 per cent) Thus, the inhibition produced by enterogastrone if applied in the first period is much greater than that of urogastrone

Sympathetic innervation of the cat's footpad HARRY D PATTON (introduced by Curt P Richter) *Psychobiological Lab, The Johns Hopkins Hospital, Baltimore, Maryland* Specific sympathetic effector systems are usually studied by nonobjective qualitative techniques Sweat-gland activity, however, may be studied objectively and quantitatively in cats utilizing electrical responses of footpad sweat glands ("galvanic response") induced by single shock stimulation of the ipsilateral sympathetic chain The responses are recorded on a string galvanometer through Zn ZnSO<sub>4</sub> electrodes attached to the central footpad and the shaved contralateral thigh

As part of a general study of sudomotor nerves using this method information was obtained concerning innervation of the hind foot (a) postganglionic outflow (b) minimal range of ganglia innervated by single preganglionic fibers

The postganglionic outflow was determined by severing the chain immediately below each ganglion from L<sub>4</sub> to S<sub>2</sub> The separate ganglia were stimulated through the stump of chain above them In 9 cats responses were obtained from L<sub>6</sub>, L<sub>7</sub> and S<sub>1</sub>, in 1 cat from only L<sub>6</sub> and L<sub>7</sub> Quantitative contributions of each ganglion varied from animal to animal corresponding no doubt to variations in the constitution of the lumbosacral plexus L<sub>7</sub> consistently gave largest responses

Distribution of preganglionic fibers to the three ganglia was determined by comparing magnitudes of responses obtained from maximal stimulation of segments of the intact lumbar chain Since the lumbar chain consists of descending preganglionic fibers, reduction of response in passing caudally along the chain indicates termination of fibers in the preceding ganglion The results indicate that each sudomotor preganglionic fiber supplies at least two ganglia No neuronal path for strictly segmental sudomotor discharge was found

Effect of environmental temperature changes on the living white mouse spleen HAROLD M PECK (introduced by Karl H Beyer) *Dept of Anatomy, Western Reserve Univ, Cleveland, Ohio, and Dept of Pharmacology, Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa* The anatomy and physiology of 300 normal living white mice spleens were observed by the quartz rod illumination technique devised by Knisely, (1), (*Anat Rec* 64 499, 1936) Particular attention was paid to the red pulp tissue areas The chamber and small thermometer used in these experiments permitted complete immersion of the spleen in Ringer's solution and very close temperature regulation The methods of Knisely, (2), (*Anat Rec* 65 23-50, 1936) and MacKenzie, Whipple and Wintersteiner, (3), (*Am J Anat* 68 397, 1941) were duplicated as closely as possible

There was much intermittent sinusoidal storage and activity, with intermittent circulation, as previously described by Knisely, (2), at temperatures of 35-36°C

Decreased sinusoidal activity, few sinusoids in storage, an active, relatively constant circulation with most of the vessels open and active, similar to that reported by MacKenzie, (3), were noted at temperatures of 38-39°

Whereas the anatomical integrity of the splenic vessels was not altered, the rate of blood flow, and number of functioning blood vessels were increased and periodic sinusoidal activity was decreased as the temperature was elevated from 35° to 39°C

Successful production of secondary deciduomata B M PECKHAM (by invitation) and R R GREEVE *From the Dept of Physiology, Northwestern Univ Medical School, Chicago, Illinois* It has been claimed that the presence of deciduo-

mata partially inhibits (Selye and McKeown, 1935) or prevents (Atkinson and Leatham, 1945) the formation of further (secondary) deciduomata. Other workers state that such is not the case (Rothchild and Meyer, 1942) or say that by special treatment secondary deciduomata can be produced (Lyon and Allen, 1943). It was decided, therefore, that further experimental work on this subject would be of interest.

Ten adult albino rats of the Sprague-Dawley strain were castrated in estrus and given 10 mg of progesterone daily to sensitize their uteri for the deciduomal reaction. On the fourth day the right uteri of all animals were traumatized by threading. On the eighth day the presence of primary deciduomata was observed and their left uteri were threaded. All animals were sacrificed on the twelfth day.

Secondary deciduomata were found in nine of the ten animals.

It is obvious that the presence of primary deciduomata in the uteri of the castrate rat does not prevent the formation of secondary deciduomata.

**Chronic toxicity of hexachlorocyclohexane and its gamma-isomere (Gammexane) in rats**  
KENNETH E. PENROD, *Dept. Zoology and Entomology, Iowa State College and Dept. Physiology, Boston Univ. School of Medicine, Boston*. Both hexachlorocyclohexane,  $C_6H_6Cl_6$  (also known as "666"), and its gamma isomere, known as Gammexane, are in increasing use as insecticides. The effect on laboratory rats of continuous ingestion of sublethal doses over considerable periods of time has been investigated. The maximum tolerated dose was about 0.075% for Gammexane and 0.15% for "666" when mixed with ground feed *ad libitum*. Thus the relative toxicities found were 2:1, although as an insecticide the gamma isomere is generally considered to be the only active component of any consequence. This isomere makes up approximately 10% of the crude "666".

No evidence for any tolerance development to either the "666" or Gammexane could be shown by working up from smaller doses. The amount of voluntary exercise was not significantly affected until the animals were very near collapse. Moreover, no constant effect on gastro-intestinal motility could be shown.

Data are not yet available on which to judge regarding effects on reproductive indications, however, that either, the ability to conceive and to care for the young after birth are seriously impaired.

**The effect of pentothal sodium on blood gas tensions**  
KENNETH E. PENROD and A. H. HARRIS, *Dept. Zoology, Boston Univ. School of Medicine*. It has been noted that the arterial  $O_2$  content dropped markedly following the anesthetic. Since to our knowledge no reference to this fact was available, it was decided to investigate the phenomenon further.

In one series of 12 dogs the arterial  $O_2$  content fell an average of 3.1 vol % (18.7 to 15.6) following single or two-stage intravenous injection of 5% pentothal sodium to the stage of deep narcosis. The concomitant arterial  $CO_2$  contents showed a rise of 6.3 vol % (36.8 to 43.1). However, in view of the shape of the oxygen dissociation curves, this degree of respiratory depression does not fully account for the fall in  $O_2$  content of arterial blood. Hence a second series of dogs was given artificial respiration by a mechanical respirometer, beginning as quickly as possible after the first pentothal injection. The fall in arterial  $O_2$  content averaged 1.6 vol % and the arterial  $CO_2$  content was likewise lowered on an average of 1.1 vol %, indicative of a degree of slight overventilation.

Hematocrit studies in the second series revealed a fall of 9% following pentothal injection. Since the fall in arterial  $O_2$  content amounted to 11.7% in this series it can in all probability be ascribed largely to changes in the hematocrit, either from plasma dilution or red cell storage, or both. The hematocrit change as well as the reduction in arterial  $O_2$  content can be effectively opposed by injection of 0.5 cc of 1:1000 epinephrine. [This work was supported in part by a contract, W33-038 ac 14757, with the Aeromedical Laboratory, Air Materiel Command, AAF, Wright Field, Dayton, Ohio.]

**A sudden fall in the skin temperature of denervated or sympathectomized paws exposed to cold**  
JOHN F. PERKINS, JR., and MAO-CHIH LI (introduced by E. M. Landis), *Dept. of Physiology, Harvard Medical School, Boston, Mass.* A sudden, continued fall in the skin temperature of denervated or sympathectomized paws exposed to a cold environment has been repeatedly observed in one unanesthetized dog and in 31 cats lightly anesthetized with nembutal. The temperature declines to approximately the same value as that of the normally innervated paws, rising abruptly if the surrounding air is warmed.

This sudden vasoconstriction does not occur unless the skin of the vasodilated paw is cooled to a certain apparently critical or "threshold" temperature, whose value tends to be higher the longer the interval after denervation, ranging from 24° to 26°C two days after denervation to 28° to 30°C seven to fifteen days after. With longer intervals, there is a gradual, rather than a sudden, fall in skin temperature. Following preganglionic sympathectomy the "threshold" temperature remains approximately constant at an average value of 23° ± 3°C (dog) from seven days after operation until regrowth occurs.

Removal or denervation of the adrenal glands does not abolish the phenomenon, nor does acute amputation of all tissues of the leg except artery and vein, to which procaine was applied. Tetraethyl ammonium bromide and small doses of nembutal, given intravenously shortly after the start of the sudden fall in skin temperature momentarily abolish the vasoconstriction.

Other factors having been excluded, it is suggested that this sudden vasoconstriction results from increased sensitivity to cold on the part of the blood vessels themselves or of residual nerve fibers in close relation to the arteriovenous anastomoses.

**A method for introduction and use of a flexible plastic arterial catheter of small diameter.** L. H. PETERSON (introduced by H. C. Bazett) *Univ of Pennsylvania Medical School*. A syringe adaptation is shown which will allow the introduction of a plastic tube 12 cm. long, 0.45 mm. O.D., and 0.21 mm. I.D. into the lumen of an artery under sterile conditions without causing hematomas, or introducing clots into the artery. This method allows the direct recording of blood pressure under a greater variety of circumstances than is possible with a steel needle. The method is adaptable for introducing fluids, within the limits imposed by viscosity, into the blood stream or withdrawing blood from the vessel, inasmuch as blood does not easily clot in the tube.

The adapted syringe consists of a hollow steel plunger ground to fit a common 10 cc. tuberculin syringe connected to a manometer at one end and with a nipple for the plastic tube at the other. The fluid column (6% citrate) transmitting pressure then extends from the open end of the plastic tube to the manometer diaphragm. The syringe outside the tube is filled with physiological saline. Thus the tube immersed in saline is "injected" into the artery. The needle used with the syringe is a specially drawn steel tube, 0.68 mm. (22 gauge) I.D. 0.52 mm. (20 gauge).

Provided that the volume displacement of the manometer is small, the time characteristics of the system are good. A Lilly manometer (displacement  $10^{-6}$  cc./100 mm. Hg.) so connected has a natural frequency of about 80 CPS. [Supported by a contract from the Office of Naval Research.]

The amounts of connective tissue in various muscles of the dog with some interspecific comparisons. NAOMI E. PETTENGILL (by invitation) and ARTHUR W. MARTIN, *Dept. of Physiology and Biophysics, Univ. of Washington, Seattle*. General estimates of the amount of muscle tissue in an animal are too high by the amount of metabolically-inert connective tissue contained therein. We believe that the amount of connective tissue is not negligible for many physiological studies.

Samples of muscle freed of tendon were hydrolyzed with 0.1 N NaOH solution until no biuret test could be secured from the supernatant. The dry weight of the collagen and elastin was determined and corrected to wet weight by the use of the factor 0.37.

Within a species the connective tissue content of different muscles may be significantly different. Some average values for the dog are: masseter 9.5%, diaphragm 7.0%, deltoideus 5.4%, sternocephalicus 4.8%, temporalis 3.4%, and sternothyroid 2.3%, each being significantly different from a majority of the rest. Rabbit, rat and hamster show the same type differences.

Between species of different body size it may be stated as a tentative rule that homologous muscles will differ significantly in connective tissue content. For example if the per cent connective tissue in diaphragm is compared we find: dog 7.0%, rabbit 5.3%, rat 5.0% and hamster 4.0%. Other muscles may be similarly arrayed. However, bodily configuration or mode of life may upset the generalization. The gastrocnemius of the hamster (100 grams) contains 5.7% connective tissue as compared with 3.4% for the rat (250 grams). It is possible that entire species will be out of line with the generalization. Further observations will be made to extend our knowledge of this relationship.

Some observations on the effect of thiouracil and dinitrophenol on the chick metabolic rate. CHARLES S. PETTY (by invitation) and ARTHUR W. MARTIN, *Dept. of Physiology and Biophysics, Univ. of Washington, Seattle*. Chicks (38) were fed at four levels of thiouracil (0.00%, 0.10%, 0.15%, 0.20%) for four months at which time the BMRs were determined. A significant increase over the controls was found, the amount paralleling the increase in thiouracil level. At 0.15% thiouracil there was about 6% increase, on 0.2% nearly 14% increase. Dosage levels of two groups were then raised, 0.10% to 0.30% and 0.15% to 0.40%. After 9-15 days the BMRs were again determined but no significant decreases in metabolic activity were observed.

The metabolic reactions to 15 mgm./kgm. of 2,4-dinitrophenol was then tested and all chicks responded with an increase in metabolic activity amounting to 80-100%.

Upon sacrifice of the chicks a tremendous hypertrophy of the thyroid glands in the thiouracil treated chicks was noted. In control chicks the total thyroid tissue averaged 0.073 mgm./gm. body weight, on the various dosages of thiouracil from 0.66, on the low dosage to 3.4 mgm./gm. at the highest level. The degree of hypertrophy may help to explain the increase in BMR.

Young chicks were tested to see if DNP cataract could be affected by administration of thiouracil. After maintenance for about 6 days on two



levels of thiouracil (0.15% and 0.30%) two levels of DNP (0.10% and 0.15%) were employed to cause cataract. The incidence was not lowered by thiouracil administration but the rate of onset of cataracts was definitely slowed and the thiouracil chicks survived the DNP poisoning better than the controls.

**Estrone oxidation products** A comparative study of estrone, marrianolic acid and estrolic acid. GREGORY PINCUS *Worcester Foundation for Experimental Biology, Shrewsbury, Mass.* Marrianolic and estrolic acids are actahydrophenanthrene derivatives, the former obtained after potassium hypiodite oxidation of the bezozyl ether of estrone and the latter after peracetic acid oxidation of estrone acetate. In the Allen-Doisy test marrianolic acid has an estrogenic activity approximately equal to that of estrone whereas estrolic acid has about 1/100th the activity of estrone. In the Astwood uterine water assay marrianolic and estrolic acids are approximately 1/200th as active as estrone. Estrolic acid is as active as estrone as an inhibitor of pituitary gonadotrophin, but marrianolic acid is much less active. Estrone causes the release of pituitary corticotrophin, estrolic acid does not. The relationship of the activity of these compounds to their molecular structure will be discussed [Aided by a grant from G. D. Searle and Company].

**Correlation of pancreatic secretion and the pH of the duodenal content** I. J. PINCUS (by invitation) and J. E. THOMAS *Dept. of Physiology, Jefferson Medical College, Philadelphia, Pennsylvania*. Experiments were performed on three dogs provided with gastric and duodenal fistulae, the latter advantageously placed so that glass canulae could be introduced into the main pancreatic duct. pH of the duodenal content, withdrawn from a point three inches beyond the ostium of the pancreatic duct, was determined at intervals after the animals were fed various food stuffs.

The effect of pancreatic juice upon the pH of the duodenal content was studied by comparing the results obtained when the juice was excluded from the intestine with observations made when the juice was reintroduced into the duodenum. It was found that in the mid-duodenum the pH of the intestinal content when juice was excluded did not drop below minimal values obtained when the juice was re-introduced, however it was generally more acid. These findings suggest that the acid gastric juice was partially neutralized by succus entericus or bile but that more complete neutralization was generally obtained when pancreatic juice was present.

The effect of the acidity of the duodenal content upon the volume of secretion was studied by noting the volumes secreted in ten minute periods and the pH of duodenal content withdrawn during the

same period of time. The expected correlation between volume and pH was, generally, not apparent although with greater volumes the pH of the duodenal content tended to be low. It would seem that this factor can be assigned only a secondary role in determining the amount of juice secreted by the pancreas in response to food.

**The nature of the human renal mechanism for acidifying the urine** R. F. PITTS, W. D. LOT SPEICH (by invitation), J. L. AYER (by invitation) and W. A. SCHIESS (by invitation) *Dept. of Physiology, Syracuse Univ. College of Medicine, Syracuse, New York*. The rate of excretion of titratable acid has been measured in a series of experiments on four normal human subjects rendered acidotic by the ingestion of ammonium chloride. When sodium phosphate is infused in quantities sufficient to cause the excretion of 0.4 to 0.6 millimols of this buffer per minute, the rate of excretion of titratable acid increases to 0.3 to 0.45 milliequivalents per minute. This acid might be derived either from filtered carbonic acid or from filtered monobasic phosphate, the only two acids present in the filtrate in significant quantities, or it might be added to the filtrate by a secretory mechanism localized in the renal tubular cells. This latter mechanism has been shown to be the significant one by exclusion. Thus, the filtration of carbonic acid can account for only  $\frac{1}{4}$  to  $\frac{1}{3}$  of the excreted acid, the filtration of monobasic phosphate can account for only  $\frac{1}{6}$  of the excreted acid. Therefore, the renal tubular cells must add acid to the urine. This view has been confirmed in experiments in which creatinine has been infused to cause the excretion of large quantities of buffer. The human renal mechanism for acidifying the urine is thus qualitatively similar to that described previously in the dog (Pitts, R. F. and Alexander R. S., *Amer. J. Physiol.* 144: 239, 1945) [Aided by grants from the John and Mary R. Markle Foundation and the U. S. Health Service].

**A study of the behavior of various gases when placed in the colon of man** ROBERT S. POGRUND (by invitation) and F. R. STEGGERDA *Dept. of Physiology, Univ. of Illinois, Urbana, Illinois*. The absorption rates of oxygen, carbon dioxide, and nitrogen were studied by the introduction of these gases through a rectal tube inserted in colons of adult male subjects. After the lapse of definite intervals of time, small volume samples of the gas were withdrawn and analyzed for oxygen, carbon dioxide, methane hydrogen, and nitrogen.

Carbon dioxide is the most readily absorbed gas, oxygen next, and nitrogen the least. Gas absorption has been shown to follow the physical laws of diffusion, the end point of which must be in equilibrium between the injected gas and the gases of the venous blood, so that in addition to the ab-



sorption of gas, there is also an entrance of gases from the blood into the lumen of the colon

The results obtained show that the oxygen contained in air is absorbed at a rate in which an equilibrium value is reached within four hours, while carbon dioxide in a mixture with nitrogen attains equilibration in less than an hour. Nitrogen is not absorbed to any great extent, but diffusion of this gas from the blood is considerable under certain conditions

Cyclic variations in the concentration of copper reducing substances in cervical secretions. W. T. POMMERENKE (introduced by Wallace O. Fenn) *The Univ. of Rochester School of Medicine and Dentistry*. The cervical mucus of normal menstruating women undergoes a tenfold increase in production at midcycle when ovulation is believed to occur. At this time the mucus possesses its highest water content, lowest cell count and viscosity, and is most readily penetrable by spermatozoa. Free reducing substances, expressed as glucose, are present throughout the cycle, the highest concentration being noted before and after the ovulatory phase. Upon hydrolysis additional quantities of reducing substances are found. The glycogen concentration in cervical mucus likewise undergoes cyclic variations. The sugars studied are present in lowest concentration at midcycle even when the calculations are made on a dry weight basis. However, when one considers the marked increase in quantity of cervical mucus which is produced at midcycle, it becomes apparent that the greatest amount of sugar is present at this time. Other reducing substances than sugars are also present. Color reactions characteristic of tyrosine and tryptophane and cystine may be obtained directly from cervical mucus. The presence of certain amino acids may contribute to the total amount of reducing substances that are recoverable. Spermatozoa require utilizable sugars for their prolonged activity and glycolysis and since they probably carry with them no appreciable extracellular nutritive material when they penetrate the cervical mucus, it is suggested by these studies that they find in their new environment a medium suitable for their metabolism and activity.

Human tolerance to high positive acceleration of short duration. J. R. POPPEN, and D. T. WATTS (introduced by D. W. Bronk) *Naval Air Experimentol Station, Philadelphia 12, Pa.* Experiments have been conducted showing that average individuals can safely tolerate the acceleration necessary for the use of the ejection seat for escape from high performance aircraft. Volunteer subjects, fastened in an aircraft seat with lap and shoulder harness, were ejected up a test tower by means of powder operated catapults. Velocity, catapult pressure, seat acceleration and

acceleration on subjects' hip, shoulder and head were recorded on a multi channel oscillograph.

It was estimated vertebral injury would occur in the lumbar region at vertical acceleration of 23 to 25 G. After preliminary experiments at progressively increasing accelerations 52 ejections were made with 21 individuals using a standardized charge designed to change the acceleration of the seatman mass at approximately 100 G/sec with a maximum of 18 to 20 G. Average maximum accelerations recorded on the seat, hip, shoulder and head were 17.4, 18.0, 18.5 and 17.0 G respectively. Catapult strokes of 40", 52" and 60" gave average ejection velocities of 55.4, 63.4 and 69.5 ft/sec respectively. Total duration of acceleration was 0.15 to 0.25 sec. Subjective reactions have been mild pains in the buttocks, lumbar, thoracic or cervical regions. No injuries have occurred.

Experiments with varied rates of acceleration have shown that the G recorded on the subject compared to that on the seat becomes progressively greater as the rate of acceleration is increased above 100 G/sec. This is to be expected due to the dynamic load factors between the centers of gravity of seat and man.

Increase in irritability of mammalian nerve in situ following ischemia. E. L. PORTER and P. S. WHARTON (by invitation) *Dept. of Physiology, Univ. of Texas School of Medicine, Galveston, Tex.* A cat has brain and cord pithed. The tibialis anticus muscle records its contractions on a slow drum. The peroneal nerve is exposed at the knee for 3 cm. The distal branches of this nerve innervating extensor muscles of the foot are ligated as a group leaving only the small branch to the tibialis anticus muscle. Lifting the nerve by the ligature the minute blood vessels supplying the nerve near the tibialis anticus muscle are visible. They are freed sufficiently so that a small bulldog clamp may be applied to them. A glass electrode (Porter, A. 53-497, 1917) is applied to the upper end of the nerve and filled with Ringer's solution. The circulation in the nerve is observed through the glass electrode with a strong lens. The nerve is stimulated once in three seconds to cause near minimal contractions of the muscle. The bulldog clamp is now applied to the blood vessels of the nerve and the circulation in the nerve is observed to stop. After a latent period (one to five minutes), the contractions on the drum increase markedly in height, reaching a maximum after several minutes. On removal of the clamp the circulation in the nerve is resumed. The muscle contractions gradually during some minutes return to approximately the original original height. The blood supply to the muscle has not been interfered with. The increased con-

traction height is therefore due to a change in the nerve at or near the point of stimulation

**A convertible kymograph with synchronous motor, and a timing pendulum for universal driving current** W T PORTER and F H PRATT *Dover and Wellesley Hills, Massachusetts* The kymograph, driven by a self-starting inductor motor, is adapted to either single cylinder or long-paper use The range of 13 speeds is from 1 revolution in 12 hrs up to 1 revolution per second, with directly selective intermediate stages The motor will carry even the long paper quietly and evenly at high speed for over an hour

The pendulum is actuated each second by the mutual attraction of two opposed electromagnets, one of which, together with a mercury switch, is integral with the pendulum Power can be drawn equally well from an a c or d c line, or from a battery, while the signal output of selective periods can be taken at will from line or relay Continuous operation under a transformer can extend into many weeks (cf Pratt, *Fed Proc* 3 37, 1944)

**Oxygen requirements of the neurones in sympathetic ganglia** J M POSTERNAK<sup>1</sup> (by invitation), M G LARRABEE, and D W BRONK *Johnson Foundation, Univ of Pennsylvania* The rate of oxygen consumption of a sympathetic ganglion is measurably increased when the pre-ganglionic nerve is stimulated at rates as low as 3 per second The consumption further increases with frequency of stimulation up to approximately a doubling (as previously reported) at about 15 per second There is not much further increase with more rapid stimulation, possibly because the ganglion cells fail to respond to each volley of presynaptic impulses

A small burst of oxygen consumption can be recorded after as few as two or three volleys of impulse The increased rate of consumption lasts no longer than 15 seconds, and may be much shorter since there are technical limitations to the speed of measurement

In these experiments the oxygen consumption was determined by measuring the oxygen tension with a tiny, suitably-polarized platinum electrode thrust into the ganglion and then observing the rate of fall of tension when perfusion was abruptly stopped

When perfusion is stopped, the oxygen tension within a sympathetic ganglion falls to zero or a very low value in less than a minute The number of ganglion cells responding to a volley of pre-ganglionic impulses at first is either unchanged or else is increased for ten or more minutes, after which there is a progressive decline in response

The mechanisms of the initial increase in response which sometimes occurs has been investigated by comparing the effects of perfusion with oxygen free solutions and with oxygenated solutions containing metabolic poisons

Further studies concerning the role of the diet in the production of nephrosclerosis and hypertension by anterior pituitary preparations J LEAL PRADO<sup>1</sup> (by invitation), PAUL DONTIGNY<sup>2</sup> (by invitation), ELLANOR HAY and HANS SEIPE *Institut de Medecine et de Chirurgie experimentales, Universite de Montreal, Montreal, Canada* In continuation of our earlier pertinent experiments, we examined the effect of various synthetic diets upon the nephrosclerosis, hypertension and adrenal enlargement, caused by lyophilized cattle anterior pituitary tissue

Experiments on hooded male rats (sensitized by unilateral nephrectomy, castration and a high Na Cl diet) indicate that on synthetic diets, in which the protein (casein) concentration is 15%, the anterior pituitary preparations cause negligible (or no) nephrosclerosis, adrenal enlargement and hypertension On the other hand, diets containing 30% protein are highly effective in rendering the animals sensitive to all three of these manifestations of pituitary overdosage It is especially noteworthy that the nephrosclerosis and adrenal cortical enlargement, produced under these conditions, roughly parallel the increase in blood pressure

The theoretic interpretation of these effects will be discussed with special emphasis upon the possible rôle of the vitamin (and particularly the choline) content of the diet, since the addition of liberal vitamin (and particularly choline) supplements to high protein diets tends to diminish the toxicity of the lyophilized anterior lobe preparations [*Subsidized by a grant of the Commonwealth Fund*]

**The clinical sequence of radiation damage** C L PROSSER, E E PAINTER and M N SWIFT (by invitation) *Argonne National Lab, Chicago, Illinois, Univ of Illinois, Urbana, Illinois and Loyola Univ School of Medicine, Chicago, Illinois* The patho-physiological effects of radiation in animals depend upon the total dose, the dose rate and the time after exposure The general features of the clinical course are similar whether ionization is caused by penetrating external radiations or by alpha or beta rays from internally deposited radioactive materials At very high dose rates of X rays (several hundred roentgens per minute) guinea pigs may die during exposure (Henshaw) At lower dose rates (50 to 800 r total body at 5-15 r per minute) some rabbits and chickens die within

<sup>1</sup> Fellow of the Swiss Foundation for Medical Biological Studies

<sup>1</sup> Fellow of the Canada Brazil Trust Fund  
Fellow of the Canadian National Research Council

day while most animals show early signs of radiation sickness. This is usually characterized by prostration, decreased food and water consumption, gastro intestinal disturbances, and in the rabbit, granulocytosis and a marked fall in blood pressure. Early acute deaths may occur at 4 to 6 days in the dog and rat with dehydration. Most acute deaths occur in different species with each type of radiation at 9 to 21 days after treatment. The syndrome includes leucopenia, diminished intestinal absorption, excessive destruction of red cells, tissue breakdown, liver dysfunction and other alterations. Terminally the animals show nonspecific symptoms of severe toxemia.

At still lower dose rates (e.g., 12.5 r of X-rays per day in dogs or low doses of plutonium or strontium<sup>90</sup>) subacute deaths (in dogs, rabbits, rats and mice) occur after several months of exposure. These may be due to anemia or extreme emaciation. At doses of 1.0 r or less of X-rays per day or with small amounts of deposited radioactive materials chronic deaths occur in mice and rats after about 200 days. Many of these deaths are caused by tumors.

An epinephrine-like catechol compound in the brain. W. RAAB (introduced by F. J. M. Siegel) *Division of Experimental Medicine, Univ. of Vermont, Burlington, Vermont*. Relatively high concentrations of an epinephrine like catechol compound were found in the brains of rats and dogs, both by colorimetric (modified method of Shaw) and biological tests in dialyzates of brain tissue. The highest concentrations were found in the big ganglia (corpus striatum, thalamus and hypothalamus), smaller amounts in the cortex and still smaller amounts in the subcortical white matter and corpus callosum.

An average increase of 16 per cent in the total rat brain occurred following injection of epinephrine (2.5 microgram/gram) and a diminution of 24 per cent following adrenalectomy. Large doses of insulin gave rise to an increase of 28 per cent, thyroxin had no significant effect.

In human suboccipital cisternal fluid the average concentration was more than twice that found in the lumbar fluid.

The epinephrine like material isolated from the brain by dialysis was equal to epinephrine in vasoconstrictor activity but differed from it in the following respects: no intensification of the blood pressure effect through cocaine, weakening but not inversion of the blood pressure effect through ergotamine, constriction of the rabbit's intestine, inhibition of the frog heart, lower "denominator of specific ratio" (Shaw's method).

Pending further chemical identification the term "encephalin" is proposed for the substance in question.

The gut constricting properties of the cerebro

spinal fluid (Dixon, Trendelenburg) and the appearance of a gut constricting substance in the blood in anxiety states (Milhorat et al.) suggest the identity of this latter substance with encephalin which is believed to be fundamentally involved in the psychosomatic aspects of emotional patterns. [This study has been supported in part by a grant from the John and Mary R. Markle Foundation.]

**Alveolar gas changes during breath holding**  
H. RAHN, A. B. OTIS, and WALLACE O. FENN  
*Dept. of Physiology, University of Rochester School of Medicine and Dentistry, Rochester, New York*. With inspired oxygen tensions ranging from 70 to 700 mm Hg, the alveolar oxygen and carbon dioxide concentrations, and arterial saturation by the oximeter were recorded for 8 subjects before breath holding and at the breaking point.

During apnoea the oxygen uptake from the lung is normal at high  $O_2$  tensions, but falls to 25% at the lowest tensions (18,000 ft altitude). As most of the  $CO_2$  is retained by the blood and tissues higher oxygen tensions give rise to alveolar  $R/Q$ 's as low as 0.1. When the  $R/Q$  is less than 1.0 the lung volume decreases. If  $N_2$  is present this results chiefly in an increased  $pN_2$  and a rapid decrease in  $pO_2$ . When no  $N_2$  is present the volume decrease chiefly prevents a fall in  $pO_2$ , so that the  $pCO_2$  is much higher at the breaking point for the same initial alveolar  $pO_2$ .

The alveolar  $pO_2$  and  $pCO_2$  are the principal stimuli which determine the breaking point. While these two are additive, the oxygen factor becomes negligible at high  $O_2$  tensions and the carbon dioxide factor at low  $O_2$  tensions.

Application of Gray's Multiple Factor Theory indicates that the breaking point occurs when the total stimulus from  $CO_2$  and  $O_2$  induce an alveolar ventilation ratio of 8. Acclimatization to an altitude of 10000 ft for several weeks (three subjects) changed the breath holding values in such a way as to indicate an increased sensitivity of the respiratory center to  $CO_2$  and a decreased sensitivity to  $O_2$ . [Work done under contract with Air Materiel Command, Wright Field.]

**Reflex sweating responses and the influence of arterial occlusion upon sweat gland activity**  
WALTER C. RANDALL *Dept. of Physiology, St. Louis Univ. School of Medicine, St. Louis, Mo*. The sweat glands may be stimulated reflexly by application of heat to one side of the body even though blood flow to the heated area is occluded. It is demonstrated therefore that purely reflex sweating may occur, and that this does not necessarily involve an increase in blood temperature at sweat centers in the CNS. Such reflex responses of the sweat glands are relatively diffuse and not confined to specific dermatomes.

During profuse sweating in a warm environ-

ment, the brachial artery on one side was occluded and sweating responses on both forearms studied. Although sweating did not immediately cease on the occluded arm the number of functional sweat glands progressively decreased over a period of 20 to 30 minutes. Neither was cyclic sweating abolished, but each peak was marked by fewer sweat spots. As soon as sweating had thus declined to low levels, radiant heat was applied directly to the area, and following a short delay, during which skin temperature in the area rose rapidly, high peaks of sweating were observed. Similar peaks of sweating could be induced reflexly by application of radiant heat to the opposite, non-occluded arm for at least 20 minutes following occlusion. Typical cyclic sweating continued on the normal, non-occluded arm throughout the experiment. Thus it is established that although sweating may progressively decline and finally stop after prolonged occlusion, the sweat glands themselves are not exhausted since they will respond to relatively strong stimulation for a period of at least 30 minutes following occlusion.

**Non-effect of hysterectomy on the ovary**  
BROOKS RANNEY (by invitation), B M PECKHAM (by invitation) and R R GREENE *From the Dept of Physiology, Northwestern Univ Medical School, Chicago, Illinois*. For years there has been controversy concerning a postulated influence of the uterus on ovarian function. To study this Shelesnyak and Schwarz (1944) hysterectomized twenty-two day-old rats and sacrificed them six to twenty one weeks later. They reported that ovaries of experimental animals showed a "uniform picture"—(1) fluid within ovarian capsules, (2) red, swollen ovaries, apparently larger than control ovaries, though no significant weight differences were found, and (3) microscopically, "marked luteinization and depressed follicular development" in experimental ovaries.

This experiment was repeated using fourteen hysterectomized rats and fifteen controls. To rule out a possible effect on ovarian function conceivably resulting from fluid pressure within the reported capsular cysts, additional groups of fourteen decapsulated and fifteen hysterectomized, decapsulated rats were included. Rats were operated upon at twenty-two days and were sacrificed and examined sixteen weeks later. Vaginal smears from each animal, examined daily for two weeks preceding autopsy, showed equal physiological responses to endogenous ovarian hormones in all four groups. Ovaries were fixed, weighed and examined microscopically. No significant group differences in mean ovarian weights were demonstrable, nor were ovarian weights of those five hysterectomized rats which developed unilateral cysts of the ovarian capsule significantly larger. Microscopically, the appearance of corpora lutea,

follicles, vaginal mucosa and endometrium (when present) in all four groups varied only with the stage of cycle during which each animal was sacrificed.

In summary, no significant functional or microscopic differences were observed between the ovaries of hysterectomized rats and those of control rats.

**Purification of the substance which is responsible for the vasoconstrictor activity of serum**  
MAURICE M RAPPORT (by invitation), ARDA ALDEN GREEN (by invitation) and IRVINE H PAGE *From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio*. A highly active vasoconstrictor preparation has been obtained from beef serum by the following method. The proteins are precipitated at acidic pH with ethanol and removed by filtration. The filtrate is concentrated to a small volume and inactive material is precipitated with acetone. After evaporation of the acetone, extraction with chloroform removes another inactive fraction. The aqueous phase is then saturated with ammonium sulfate and extracted with butanol. The active material is precipitated from the butanol as a crystalline diluturate.

The vasoconstrictor activity has been followed by means of the isolated rabbit ear perfused with a modified Ringer solution. Some chemical properties of the preparation will be discussed.

**The human sensorimotor cortex as studied by electrical stimulation**  
THEODORE RASMUSSEN (by invitation) and WILDER PENFIELD *Dept of Neurology and Neurosurgery, McGill Univ, and the Montreal Neurological Inst*. An analysis was made of the responses produced by stimulation of the human cortex in 206 operations performed under local anesthesia. With a few minor changes and additions, the previous analysis by Penfield and Boldrey (*Brain* 60: 389-443, 1937) was corroborated.

Sensory responses for the extremities were contralateral, but in the face area 10 per cent of the stimulations resulted in bilateral or ipsilateral sensation. These points were all situated in the anticipated sensory sequence and frequently were adjacent to loci producing the usual contralateral responses pertaining to that part. It may be pointed out that head and neck responses were found between the representations of arm and trunk. Furthermore, intra-abdominal sensation is localized at the lower end of the precentral gyrus, below the area for mouth and throat. The extent of this representation into the fissure of Sylvius and on to Island of Reil has not yet been determined.

Combined responses characteristically involved adjacent units in the sequence and, like responses to local strychninization, very rarely crossed the boundary between face and arm or between arm and leg.

Responses from the banks of the Rolandic fissure, elicited after excision of either the pre- or post central gyrus, were, in general, similar to those produced from the surfaces of these gyri, adjacent to the fissure. On the medial surface of the hemisphere, upper leg responses were near the surface while the toe responses were nearest the gyrus cinguli.

A comparison with results obtained in animals by the method of evoked potentials revealed certain apparent discrepancies which need further study.

Studies on sodium metabolism with a long half-life radioactive sodium isotope. PAUL REASER and GEORGE BURCH<sup>1</sup> (introduced by H. S. Mayerson). The use of a radioactive isotope entails the understanding of many physical and physiological phenomena.

With sodium 22 as a tracer an intensive investigation of the normal and abnormal aspects of sodium metabolism is underway. The evaluation of the results necessitates the consideration of purely physical factors such as dilution.

A careful analysis of the blood regression curves in 7 patients indicates a very close correlation with predicted behavior on the basis of intake and excretion. Formulae that were devised for the curves obtained are confirmatory evidence that unless intake and urinary output are carefully considered quite opposite conclusions can be drawn from blood concentrations alone.

The predictable behavior of such a substance as sodium makes evaluation of abnormal mechanisms easier although more questions are raised than answered.

This discussion will be primarily concerned with a comparison of the theoretical and the actual behavior of sodium in normal patients and in patients with congestive heart failure and chronic nephritis, the abnormal subjects showing considerable differences from the normal.

Daily blood determinations were performed and all urine voided, ascitic fluid, edema fluid, vomitus, etc. were collected and determined individually.

X-ray diffraction studies on human dental enamel. B. P. REED (by invitation) and C. I. REED. *Dept. of Physiology, Univ. of Illinois, Chicago Professional Colleges*. Previously reported X-ray diffraction data from bone of various species and of several varieties of natural apatite have yielded identical patterns. When dental enamel is examined, the pattern depends on the number of crystal columns included under the beam. The claim has been made that only after intense heating is the apatite pattern obtained from osseous materials. Powdered dental enamel, heated before and after grinding yields patterns and indices identical

with those previously reported for powdered bone and apatite. Dental enamel section taken from the surface of the tooth displays no orientation such as does the cortex of a long bone. In no pathological state has the X-ray diffraction pattern for dental enamel been found to be altered.

**Hypercalcemia and hypervitaminosis D.** C. I. REED. *Dept. of Physiology, Univ. of Illinois, Chicago Professional Colleges*. The simultaneous occurrence of these two conditions has led to great confusion about their interdependence. It is contended that they are not necessarily so related. Thirteen out of 209 dogs receiving doses of calciferol (2000 to 10,000 units per kilogram daily) developed persistent hypercalcemia ranging from 16 to 30 mgms per 100 cc of plasma, without weight loss, anorexia or polyuria. The maximum levels were attained in 30 to 60 days, depending on the average dose. Initial levels of calcemia were attained in 17 to 81 days after discontinuance of the vitamin. Thorough examination, both microscopic and chemical, 5 to 6 months after the initial level of calcemia was attained, showed no abnormality of any tissue except in two animals. In one, there was mild tubular nephritis with calcification. In the other, no micropathology was demonstrable but the calcium content of the myocardium was definitely above the range for healthy dog hearts. On the other hand, 18 dogs out of this same series died with evidence of acute vitamin D intoxication without ever displaying hypercalcemia of more than 2-3 mgms and that only transiently. All of these showed microscopic and chemical evidence of damage to the kidneys, liver and myocardium. The range of dosage was 20,000 to 25,000 units per kilogram per day. Thus, hypercalcemia and vitamin D intoxication, while usually concurrent are not necessarily interdependent. Hypercalcemia is not a reliable criterion of toxicity in the absence of other evidence.

**Electron microscopy of erythrocytes from dog blood.** C. I. REED and B. P. REED (by invitation). *Dept. of Physiology, Univ. of Illinois, Chicago Professional Colleges*. A few observations have been made on normal erythrocytes which show them to be entirely homogeneous internally. Any evidence of organized structure in the cytoplasm therefore, must represent a departure from normal state and insipient lysis. Nevertheless, it appears that certain details visible in partially lysed cells may be of significance. Cells dried too rapidly in air show crenation under the light microscope but by electron microscopy show marked folding of the surface layer while the biconcave form is still demonstrable. With too rapid drying in vacuo, the incipient stages of lysis are characterized by the appearance of very fine eosinophilic granules surrounded by homogeneous cytoplasm. With still more rapid drying in vacuo, most cells show masses

<sup>1</sup> From the Department of Medicine, Tulane Medical School.

roughly fibroblastic in form which appear to be formed by coalescence of these granules into aggregates with incorporation of amorphous non-staining material. The striking similarity of size and outline suggests that these masses are of homogeneous composition. With a still more advanced lysis, these masses tend to assume patterns characteristic for each cell. It is unlikely that these masses are of molecular proportions, but are rather patterned aggregates of hemoglobin with another component. These changes come about regardless of the method of fixation of specimens which suggests that they have structural significance.

**A modification of manual method of artificial respiration** C I REED *Dept of Physiology, Univ of Illinois, Chicago Colleges*. The subject is placed as in the official Red Cross method. The operator's hands are placed at sides of lower ribs with thumbs extending mesially, the feet are placed opposite subject's hips and the operator squats with elbows inside his own knees. The operator rocks on balls of feet, mesad pressure of knees forces hands both downward and mesially, thus compressing thorax from sides more than postero-anteriorly. Using normal subjects with recording spirometer in place, it was demonstrated that, in the same subject, the mean volume exchange was 20% better than with the older methods. Disadvantages are (1) an operator with broken arches cannot rock satisfactorily, (2) the position is awkward and grotesque. Advantages are (1) greater volume ventilation (2) less danger of costal injury (3) the operator can continue unrelieved for a longer period. One wholly inexperienced operator continued without interruption for 117 minutes.

Volume exchange in cc

Subject	Red Cross method	Modified method
1	108	119
2	77	91
3	49 (female)	63
4	91	107
5	83	93
6	131	155
7	115	160
8	156	188

**Electron microscopy of bull sperm** C I REED and B P REED (by invitation) *Dept of Physiology, Univ of Illinois, Chicago Professional Colleges*. Clark and associates reported as new observations on sperm first made by means of the electron microscope the existence of a protoplasmic cap and a brush branched tail tip. We have confirmed these observations on fresh bull sperm. In addition, a certain number of organisms in every field revealed heavy granulation throughout the protoplasmic cap. The granules were of the

order of 0.25 microns in diameter and when photographed, gave the appearance of enlarged microphotographs of intestinal villi. While the granules appeared to encroach on the sperm head, it is believed that this is due to the cap overlying the crescentic anterior border of the head. Since the granules seemed to bear no relation to methods of preparation, it was concluded that they are not artefacts. It is suggested that they may represent age changes in the cells.

Due to the methods of preparing spreads for electron microscopy, it is not appropos to attempt to give ratios of occurrence in normal sperm. Proportions varied among different samples of sperm. There are no data on which to base further deductions of functional significance.

**Effect of hydrochloric acid on the potential of the resting and secreting stomach** WARREN S REHM and LOWELL E HOKIN (by invitation) *Dept of Physiology, Univ of Louisville School of Medicine, Louisville, Ky*. An attempt has been made to reconcile the apparently conflicting reports in the literature on the relationship between gastric secretion and potential (Rehm and Hokin, *Am J Physiol* in press). On the basis of this previously reported work, one would anticipate relatively little change in the gastric potential after histamine stimulation when HCl of approximately the same concentration as that of gastric juice was in contact with the stomach. Using a technique described in the above reference, 0.16 N HCl was placed in contact with the mucosa of the resting stomach of amyotized dogs, and, after the potential had reached a relatively constant level, histamine was administered subcutaneously. This was followed by relatively little change in the potential (maximum change about 5 mV). No attempt was made to determine the secretory rate while the HCl was in contact with the mucosa. Measurements of the secretory rate after replacement of the HCl with normal saline revealed that the stomach was actively secreting HCl. Further experiments were performed in which the level of the potential of the resting stomach was determined with 0.16 N HCl in contact with the mucosa. The HCl was then replaced with saline and histamine was administered. After the secretory rate had reached a relatively high level, the saline was replaced with 0.16 N HCl. Comparison of the levels of the potentials in the secreting and resting stomach (for a given dog), when 0.16 N HCl was in contact with the mucosa, revealed that they were of the same magnitude within a few mV.

**The effect of applied current on the potential between a dead stomach and HCl** WARREN S REHM and LOWELL E HOKIN (by invitation) *Dept of Physiology, University of Louisville School of Medicine, Louisville, Ky*. It was found (Rehm, *Fed Proc* this volume) that when elec-

trical currents of magnitudes of as much as 3 or 4 milliamperes per  $\text{cm}^2$  were passed across the stomach wall, the effective electromotive force of the stomach leveled off at a value definitely above zero. Any theory attempting to account for the origin of the potential of the stomach must be able to account for the ability of the stomach to give rise to currents of these magnitudes. In order to determine the ability of a potential, originating from unequal ion mobilities, to deliver current the following method was used. Hydrochloric acid (0.16 N) was placed in contact with the mucosa of a dead stomach and appropriate electrodes were connected to this system. Under these conditions the potential was about 20 mv (serosa positive to mucosa in external circuit). An external electromotive force was connected in series with the stomach. When currents of 1 milliamperes per  $\text{cm}^2$  were passed through this system the effective electromotive force gradually decreased to zero over a period of about 10 minutes, and continued passage of the current resulted in a reversal of the electromotive force. After the circuit was broken the potential gradually increased to approximately its original value. This latter finding is evidence that the decrease in the electromotive force was not due to a decrease in the concentration of HCl in the solution in contact with the mucosa.

**The effect of applied current on the potential of the resting stomach.** WARREN S. REHM, *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.* It was shown in previous work (*Am. J. Physiol.* 139: 1, 1943) that when the stomach potential was shunted through a low external resistance the total IR drop in the circuit was essentially equal to the open circuit voltage. These findings indicate that the stomach is capable of producing more than this amount of electrical energy. Experiments were designated to determine how much electrical energy the stomach could produce. An external electromotive force was placed in series with the stomach, and under these conditions the electrical energy output would be equal to the product of the current and the effective electromotive force of the stomach. Attempts at calculating the electromotive force while the current was flowing were unsuccessful because of fluctuations of the resistance of the circuit. The effective electromotive force of the stomach was determined during a period of current flow by momentarily breaking the circuit, at intervals and measuring the open circuit voltage. With this method it was found that with current densities of about 0.5 milliamperes per  $\text{cm}^2$  the potential, after a temporary decrease, increased and reached a level near the original resting level. As the current densities increased the level of the potential decreased until, with currents of about 5 milliamperes per  $\text{cm}^2$ , the potential was reduced to

approximately zero. The rate of electrical energy output was calculated and it was found to reach a maximum when the current density was in the neighborhood of 2.5 milliamperes per  $\text{cm}^2$ .

**Comparison of the mechanisms whereby  $\text{NaN}_3$  and 2,4-dinitrophenol suppress anaerobic carbohydrate assimilation.** JOHN M. RLINER (by invitation) and S. SPIEGELMAN, *Dept. of Bacteriology, Washington Univ., School of Medicine, St. Louis, Mo.* It is well known that both  $\text{NaN}_3$  and 2,4-dinitrophenol (DNP) can inhibit the anaerobic assimilation of carbohydrate as well as many other processes (e.g., differentiation, nitrogen assimilation, enzymatic adaptation, etc.).

Recent studies (Spiegelman and Kamen, *Science*, 104: 581, 1946) with  $\text{P}^{32}$  have shown that while both agents can prevent nucleoprotein P turnover, DNP is relatively ineffective as compared with azide in depressing the acid soluble P-turnover. This finding made it difficult to understand the effectiveness of DNP in preventing the assimilation of carbohydrate which presumably involves mainly the acid soluble phosphate.

Accordingly, a more detailed comparison of the effects of DNP and azide on carbohydrate assimilation was made. If a known amount of glucose is fermented by yeast, about 25% is assimilated and cannot be accounted for by the products of fermentation. This assimilatory process is equally well inhibited by  $2.5 \times 10^{-4}$  M DNP and by  $1 \times 10^{-3}$  M  $\text{NaN}_3$ , providing these agents are present during the metabolism of the added glucose. A striking difference is noted, however, if they are added after the assimilatory process has been completed. The addition of  $\text{NaN}_3$  has no effect on the ability of a cell to retain the carbohydrate stored. The addition of DNP, however, causes a renewed evolution of  $\text{CO}_2$  which ends when the carbon recovery is virtually complete.

This indicates that the absence of carbohydrate assimilation in the presence of DNP is due, not to the ability of this compound to prevent this process, but rather to its capacity for stimulating the utilization of the stored carbohydrate. Azide, on the other hand, prevents the actual formation of the endogenous carbohydrate. This interpretation is consistent with the  $\text{P}^{32}$  data mentioned previously.

**The relation between the duration of systole, stroke volume, ventricular work and cycle length.** JOHN W. REMINGTON and W. F. HAMILTON, *Dept. of Physiology, Univ. of Georgia School of Medicine, Augusta, Georgia.* The method described recently for the calculation of the stroke volume from the pressure pulse contour indicates that the ejected volume is, all other things being equal, a function of the duration of systole. To determine whether under natural conditions, the relationship between these two factors still holds, the two



quantities were measured in some 600 dog pulse contours. In many cases the stroke volume measurement was controlled by the dye injection method.

The duration of mechanical systole is influenced by the duration of the cycle, as is well known. With quite low heart rates, however, there is little correlation between cycle length and duration of systole. The formulae of Ashman or of Bazett, therefore, do not fit our data over the whole range of cycle length.

There is a high correlation between length of systole and both stroke volume and ventricular work per beat. Duration of systole will predict these quantities (per sq M) with an average error of about 25%.

The contours of the ejection and work curves during systole suggests how these factors are related to systolic duration. As found by Wiggers, for the exposed heart, systolic duration in our intact animals is lessened by increased arterial resistance, myocardial stimulation or acute myocardial failure. It is prolonged by a decrease in arterial resistance or an increased filling of the ventricle. The influence of these factors remains when the cycle length is held constant by atropine or is corrected for mathematically [*This investigation was aided by a grant from Life Insurance Medical Research Fund*].

Application of the strain gage dynamometer to quantitative evaluation of uterine activity in experimental animals. S. R. M. REYNOLDS and I. H. KAISER (by invitation). *Carnegie Inst of Washington, Dept of Embryology, Baltimore 5, Md.* Measurement of the absolute expulsive force of the uterus can be made with the strain gage dynamometer. In its present form the technic is restricted to acute experiments, particularly where the effects of drugs or biological agents upon the uterus are being studied. It may also be applied with minor modifications to other viscera. Other techniques do not lend themselves as well to quantitative application.

The procedure is as follows: a loop of uterus is tied off and distended slightly with physiological saline. A 20 gage hyperdermic needle is attached through an adapter to a strain gage filled with saline (Statham, model PS-1G-120). The needle is inserted into the distended uterus. Records of atmospheric and uterine pressures are made photographically with a seismic oscillograph of high sensitivity. The record is analyzed by measuring with a planimeter (1) the total area under the curve for any period of time, and (2) the area under a "corrected" curve in which the bases of all active contractions have been connected. By dividing the areas so determined by the number seconds involved, and correcting for the weight uterine tissue in the loop of uterus, (and refer-

ence to a calibration chart) the average expulsive effort of the uterus per gram of tissue per second is obtained. The second measurement yields the amount which is attributable to the tonus under the conditions of the experiment, and the first measurement less the second yields that which is attributable to active uterine contractions.

Differential uterine tensions and the flow of maternal blood through the uterus during pregnancy. S. R. M. REYNOLDS. *Carnegie Inst of Washington, Dept of Embryology, Baltimore 5, Md.* During pregnancy in the rabbit, the conceptus is spheroidal until after the twentieth day. By the twenty-fourth day, the conceptus is cylindrical. The flow of maternal blood through the lateral uterine vein in the uterine wall is affected by the shape and size of the conceptus (*Amer J Physiol*, 148:77, 1947). The differential in tension between the mesial antimesial pole and the lateral margins of the conceptus is a function of the relation of the cube of the two semi axes to each other for spheres, and the squares of the semi axes for cylinders. This is seen by clearing the respective equations for tensions in the walls of hollow elastic bodies of similar shapes.

Measurements of 273 living conceptuses yielded a curve of increasing differential tension between the mesial and anti-mesial margins of the spheroidal conceptus up to the twentieth day, increasing from  $1.17 \pm 0.05$  on the twelfth, to  $2.02 \pm 0.04$  on the twentieth day. When the conceptus becomes cylindrical, the differential tension was  $1.47 \pm 0.04$ . The rate of maternal blood-flow in the lateral uterine vein diminished as the differential tension increased. The extent of decrease in blood flow in the non-distended uterus early in pregnancy when  $T_{\text{lateral}} = T_{\text{mesial}}$  and the time of maximum differential of tension on the twentieth day ( $T_{\text{lateral}} = 2.02 T_{\text{mesial}}$ ) is 43%. When the conceptus changed to a cylinder, with the decrease in tension differential noted above, the rate of maternal blood-flow was restored proportionately.

Experiments on the inactivation of pentothal. R. K. RICHARDS. *Dept of Pharmacology, Abbott Labs, North Chicago, Illinois.* In contrast to barbital which is largely excreted as such by the kidneys, the vast majority of the short acting barbiturates, including the ultra short acting evipal were shown to be destroyed in the body. The liver was proven to be the most important organ in their metabolism. It was assumed that pentothal (thiopentobarbital) is similarly destroyed. However, experimental evidence from this laboratory and other investigators definitely indicates that the liver is not of outstanding importance in the inactivation of this drug. While there was no doubt on its destruction in body, the primary site of this process has remained obscure so far. We conducted experiments in which a



0.5% solution of pentothal in ice cooled heparinized rabbit blood was injected i.v. in mice. Approximately 3 cc/kg were necessary to produce sleep in approximately 75% of the mice. If such solution is kept at this temperature, this dose does not change significantly. However, if it is incubated at 37.5%, the amount necessary for the same effect rises to 5 cc in about 15 minutes and 6 cc in 30 minutes. Longer incubation is not much more effective and leads to the appearance of a toxic factor. Neither pentobarbital nor evipal were similarly affected by blood. Plasma had very little effect upon pentothal in vitro. Human blood possesses qualitatively and quantitatively the same activity as rabbit blood. It is believed that other organs participate in the destruction of pentothal. Work on these and related problems continues.

The conducting system in human foetal hearts and implications regarding Q-T based thereon. JANE SANDS ROBB and CORNELIUS T. KILLOR (by invitation) *Dept of Pharmacology, College of Medicine, Syracuse Univ, Syracuse, N. Y.* Specialized tissue described by us in 1946 for the guinea pig heart has been found in human foetal hearts (one studied was loaned by the Carnegie Institute of Washington). The staining reaction (Masson, Mallory) is different from heart muscle, a sheath is present, very numerous terminal twigs supply limited areas. Transition from this type of cell to ordinary muscle is gradual. We still suggest that size of the area and some lack of simultaneity in onset (due to longer conducting strands leading to some islands at the base and lateral walls) along with cellular activity of the area determine QT duration. Anatomically a muscle may be a syncytium without being one functionally, for such limited adjacent areas will be refractory at the same time. If one area ceased to be refractory when contiguous areas were active, a situation leading to fibrillation would occur. Fibrillation would spread not according to anatomical syncytium but whenever a local area had ceased to be refractory. If QT is a record of relatively simultaneous depolarization and repolarization in multitudinous small areas, it is easy to see why P-R varies directly with heart size while QT does not, why QRS is of similar duration in human and beef hearts which do vary in size, why extremes of times for surface activation do not agree with the slow rate of conduction supposed to be true for ventricular muscle. According to this hypothesis the P-Q interval includes auricular, a-v nodal, Bundle, and Bundle branch depolarization. QT is limited to potential changes in ventricular muscle. [This work was supported by a grant from the Life Insurance Medical Research Fund and the Hendricks Fund.]

Variations in QT and in QT to cycle ratio

JANE SANDS ROBB and WILLIAM G. TURMAN (by invitation) *From the Dept of Pharmacology, College of Medicine, Syracuse Univ, Syracuse, N. Y.* In connection with studies being made in this laboratory the question rose whether QT could be changed at will by physiological procedures and whether experimentally more than one QT duration for a given cycle length could be produced on demand. It has long been known that vagal stimulation or administration of acetylcholine reduced QT relative to cycle and that epinephrine or accelerator stimulation had the opposite effect. In dogs, anaesthetized with pentobarbital, the QT/cycle ratio averages 50. If the vagi are stimulated the ratio decreases to 10 or less. When atropine is given and the vagi cut, the QT/c ratio averages 60-65. If, in addition, the accelerators are stimulated or epinephrine given the QT/c ratio rises even to 90 or above. If the heart is denervated in an acute experiment and some asphyxia allowed to occur the rate slows. By this means, cycle lengths comparable to those of vagal stimulation are obtained but now the QT/cycle ratio is long. If asphyxia is allowed to become extreme cycle remains long but QT shortens and this cannot be a vagal effect. While one may answer both questions in the affirmative all the mechanisms are not clear. How does vagal stimulation affect the ventricle to which it is not distributed? With slower rates and greater filling one expects a longer more forceful systole. If the short vagal QT were due to coronary vasoconstriction one would expect vagal stimulation and asphyxia to cause the same results which is only the case if asphyxia is extreme. [This work was supported by a grant from the Life Insurance Medical Research Fund and the Hendricks Fund.]

The respiratory response of the rat to hydrogen cyanide poisoning. W. A. ROBBIE (introduced by H. H. Hines) *State Univ. of Iowa, Iowa City*. Recent improvements in the measurement and control of HCN gas concentration and the development of a convenient technique for following the oxygen uptake of small mammals has made it possible to make quantitative observations of the effect of cyanide on respiration. At concentrations of 100 gammas of HCN per liter or higher the exposed rats die within an hour or less. At 70 gammas per liter they live for 2 to 6 hours, and if the concentration is reduced to 40 gammas the rats may live for several days. In exposures at the intermediate concentration the animals show a period of pronounced vasodilatation which is followed by vasoconstriction and convulsions. At the time of the convulsions and loss of consciousness the number of respiratory movements per minute drops to about one third the normal rate, and the breathing shifts to a gasping type. The amount of oxygen consumed by the animals closely parallels the

number of respiratory movements and may drop to 40% of the control level during the last hour of life of an exposed animal. If the HCN flow is discontinued after the animals have been unconscious for an hour the recovery is rapid. The number of respiratory movements is markedly increased above the normal as the carotid sinus mechanism is reactivated, and the oxygen consumption increases to the control level or slightly exceeds it, but there is no marked oxygen debt apparent. Infant rats are much more resistant to HCN than older ones.

**The influence of fasting on the peripheral utilization of sodium beta-hydroxybutyrate in the rat.** SIDNEY ROBERTS and CLARA M. SZEGO, *Worcester Foundation for Experimental Biology, Shrewsbury, Mass.* The rate of disappearance of intravenously administered sodium beta-hydroxybutyrate was studied in abdominally eviscerated, bilaterally nephrectomized male rats. The influence of liver and kidney upon the production, utilization, and excretion of this compound was thereby eliminated, so that peripheral tissue utilization *per se* could be investigated.

In most instances, the beta-hydroxybutyrate was injected into the saphenous vein immediately after operation in an amount equivalent to 32 mg acetone per 100 gm body weight. All animals were sacrificed either immediately or one hour later. Carcass and blood were analyzed for acetone, acetoacetate, and beta-hydroxybutyrate.

It was found that animals fasted 48 hours prior to operation utilized the injected substance nearly twice as rapidly as fed rats. Thus, the average rate of disappearance was about 10.5 mg acetone equivalents/100 gm body wt/hr in the fasted group, and approximately 6.0 mg/100 gm/hr in the fed group. The rate of disappearance of blood acetone bodies in individual animals after injection reflected the rate of utilization by the entire carcass of the same animals. No significant quantities of acetoacetate or acetone could be found in the blood or carcasses of either group.

The significance of these observations will be discussed. [Aided by a grant from the Society of the Sigma Xi.]

**The effect of urethane upon the erythrocyte membrane.** EUGENE D. ROBIN (by invitation), ABRAHAM DURI (by invitation), LEONARD ESMAN (by invitation) and CHESTER E. LEESE, *Dept. of Physiology, George Washington Univ. Medical School.* Fuhner and Neubauer observed that 1.04 Molar urethane hemolyzes red blood cells. Since 1.04 Molar urethane is 3.58 times as concentrated as isotonic urethane, from the standpoint of osmotic relationships it should cause crenation of red cells rather than hemolysis.

The hemolytic effect of several concentrations of urethane in water solution was noted. Hypotonic, isotonic, and hypertonic solutions up to

concentrations of ten per cent were capable of hemolyzing erythrocytes, twenty per cent solutions caused partial hemolysis, twenty-four per cent urethane and higher concentrations caused no hemolysis.

This effect was interpreted as follows. Urethane has two opposing actions on the erythrocyte membrane. Action one tends to increase the permeability of the membrane thereby allowing water to enter the cell and hemolysis to take place. Action two is due to the osmotic pressure exerted by urethane molecules in solution and in hypertonic solutions tends to draw water out of the cell. In hypotonic solutions both actions supplement each other and hemolysis takes place. In isotonic solution the hemolytic effect prevails and hemolysis still occurs. In hypertonic solutions the hemolytic effect is stronger and hemolysis occurs until a concentration of twenty per cent is reached. At a concentration of twenty per cent the osmotic effect of the urethane begins to overbalance the hemolytic effect and only partial hemolysis occurs. At a concentration of twenty-four per cent and greater the osmotic effect is stronger than the hemolytic effect and no hemolysis occurs.

This theory was tested by the addition of strongly hypertonic solutions of NaCl and KCl (equimolar) to varying concentrations of urethane. Hypotonic and isotonic urethane now caused only partial hemolysis instead of complete hemolysis. Five per cent and ten per cent urethane still had enough hemolytic effect to overcome the osmotic effect of the urethane plus the salt molecules and complete hemolysis occurred. Twenty per cent urethane plus the salt solution caused no hemolysis since the osmotic effect of the urethane and salt was now stronger than the hemolytic effect of the urethane. Since K is an intra-cellular substance and Na is an extra-cellular substance, it is felt that the only common mode of action would be osmotic protection.

This effect has been observed only in vitro since fragility tests on acutely and chronically urethanized rats have shown no change in the osmotic relationships of the erythrocyte in vivo.

**The control of sweating in working men.** SID ROBINSON, *Dept. of Physiology, Indiana Univ., Bloomington.* At an effective temperature<sup>1</sup> of 25°C the average skin temperatures of working men were about 34°C and remained practically unchanged when the work was varied in separate 90-minute experiments causing variation of their O<sub>2</sub> intake between 13 and 37 cc/kg of body weight per minute. The men's rectal temperatures and rates of sweating increased directly with increments in work intensity up to values averaging 38.5°C and 850 g/hr in the hardest work. Since skin temperature was constant in these experi-

ments the increased sweating must have been dependent upon a direct effect of internal temperature on the heat regulatory center and possibly also to stimulation of the center resulting from the increasing neuromuscular activity

In another series of 90 minute experiments the work was kept constant ( $O_2$  intake 19 cc/kg/min) while the effective temperature was varied between 10 and 32.5°C. The effective temperature remained constant during each experiment. In these tests each man's rectal temperature rose to about the same level every time, but average skin temperature and rate of sweating increased directly with increasing effective temperature in this range, the values varying from 28 to 36°C and 50 to 1500 g/hr respectively. Thus the stimulus for increased sweating here appears to depend entirely upon reflexes from the skin.

In other experiments at the same work ( $O_2$  intake 19 cc/kg/min) men's rectal and skin temperatures and rates of sweating all increased with increments in effective temperature between 32.5 and 35°C to maximal values of about 40.5°C, 38.4°C and 2000 g/hr respectively.

Evidence for a temperature-sensitive center in a poikilotherm, the turtle S. ROBBARD (with the technical assistance of L. Taylor) *From the Cardiovascular Dept., Research Inst., Michael Reese Hospital, Chicago, Illinois.* A direct relationship between the body temperature and the systemic arterial pressure has been demonstrated in the turtle, the rabbit and the chicken. It appeared to be of interest to determine whether this relationship was mediated through the direct action of the peripheral vasculature, or through the central nervous system.

Section of the spinal cord at  $C_1$  (in 8 turtles) or pithing of the brain (in 4) caused a fall in blood pressure to an average of 15/10 mm Hg. This pressure was maintained for periods up to 48 hours. Spinal reflexes reappeared almost at once. Injection of epinephrine resulted in a sharp rise in arterial pressure of the same order as that seen in the intact animal, indicating that the peripheral vasculature is capable of responding to pressor agents. However, these pithed or cord sectioned animals differed markedly from the intact animals in that cooling or warming no longer had an effect on the arterial pressure.

C	Blood Pressure	
	Normal	Pithed
	mm Hg	mm Hg
10	20/13	15/10
20	31/25	17/11
30	32/25	16/11
35	40/33	17/12

These results indicate that the turtle, a poikilotherm, has a center in the brain which is sensi-

tive to changes in body temperature. The response of this center is manifest in the changes in blood pressure attendant upon heating or cooling the normal animal.

**Body temperature-arterial pressure relationship as a basis for physiological interpretation of diurnal rhythm.** S. ROBBARD *From the Cardiovascular Dept., Research Inst., Michael Reese Hospital, Chicago, Illinois.* A direct relationship appears to exist between the body temperature and the systemic arterial pressure in amphibians, reptiles, mammals and birds. This relationship apparently depends upon the action of centers in the brain which respond to changes in temperature.

Terrestrial poikilotherms such as the frog or turtle are daily exposed to a cycle of wide fluctuations in temperature due to warming during the day and cooling at night. These external fluctuations cause increases in body temperature and activity during the day, and cooling and torpidity during night. Such large diurnal swings in body temperature and activity would appear to require a mechanism for co-ordination of metabolic activities if the animal is to survive. In the turtle, one adjustment is made through an increase in arterial pressure *pari passu* with increasing body temperature, with a return to low pressure levels as the animal cools during the night.

In the warm-blooded birds and mammals, there is a 24 hour cycle of temperature fluctuation, qualitatively similar to those seen in the poikilotherms, although this cycle is greatly reduced in amplitude. It is suggested that this diurnal temperature cycle of the homiotherms is a retention of the 24 hour temperature cycle of poikilotherms.

Some attention has previously been directed to cardiovascular variations in poikilotherms under conditions of varying body temperature, and these changes have been interpreted as passive responses. It would appear from our work that these changes are a part of a highly systematized adjustment of the animal to the cycle of body temperature changes.

**Action of anticholinesterases on axones and synapses in the cockroach, (*Periplaneta americana*).** KENNETH D. ROEDER and NANCY K. KENNEDY (by invitation) *Tufts College, Medford 55, Mass.* It has been shown (J. Neurophysiology, 10, 1947) that in the presence of  $6 \times 10^{-6}$  M DFP (diisopropyl fluorophosphate) brief stimulation of the afferent nerves entering the 6th abdominal ganglion of the cockroach results in a prolonged after discharge in giant fibers in the ventral nerve cord. Ganglionic transmission alternates from facilitation to temporary block, and does not return to normal in washing with saline. The same effect is produced by  $2.5 \times 10^{-7}$  M HTP (hexaethyl tetraphosphate), which causes a permanent synaptic block in higher concentrations. Chadwick and Hill (in press) have shown that either 5

$\times 10^{-5}$  M DFP or  $5 \times 10^{-7}$  M HTP will inhibit 90 to 95 per cent of the cholinesterase in the whole nerve cord  $10^{-4}$  M DFP or  $10^{-6}$  M HTP will cause complete cholinesterase inhibition in the cord

Conduction (spike height, velocity) and irritability of the giant fibers in the nerve cord are unaffected by the above concentrations of DFP or HTP. In the presence of much higher concentrations ( $6 \times 10^{-2}$  M DFP or  $7.5 \times 10^{-3}$  M HTP) spike potentials in the giant fibers disappear abruptly within 1-3 minutes, but in the case of DFP they return on washing with saline. The concentration causing axonic block is quite critical, lower concentrations ( $2 \times 10^{-2}$  M DFP) being without effect after 30 minutes.

While 90 to 95% cholinesterase destruction by DFP or HTP is closely correlated with irreversible synaptic instability, cholinesterase destruction seems to be unrelated to the axonic effects of these substances. It is concluded that cholinesterase plays an important and possibly conventional role in trans-synaptic conduction in insects, though the significance of its presence in axons is not clear. [*This work was made possible by a contract between Tufts College and the Army Chemical Corps*]

The effect of dibenamine on the production of irreversible hemorrhagic shock. FRANK ROEMHILD (by invitation), HAROLD GOLDBERG (by invitation), RAYMOND C INGRAHAM and HAROLD C WIGGERS *College of Medicine, Univ of Illinois, Chicago, Illinois*. The thought has prevailed for some time that perhaps the prolonged vasoconstriction induced by a severe hemorrhage may impair tissue blood flow to such a degree that extensive, irreparable damage in such organs as the liver, kidney and intestines occurs. It is thought that the latter may often be responsible for the irreversible conditions which follow. In this regard, it was decided to examine the response of normal dogs and of dogs primed with dibenamine 20 hours in advance when subjected to a 90 minute period of hemorrhagic-hypotension at 35-38 mm of Hg and following which all withdrawn blood was reinfused. Since an "adrenalin reversal" effect was obtained just prior to the onset of bleeding in the treated dogs, it is reasonable to assume that the vasoconstrictor mechanisms were still adequately blocked 20 hours after the injection of the dibenamine.

Prior to bleeding, tachycardia was present, blood pressures were at the lower limits of normality and the hematocrits were significantly lower in these treated dogs than in the control group. Whereas 84.6 per cent of the untreated dogs developed irreversible shock within the 90 minute hypotension period, only 38.5 per cent of the treated dogs failed to recover completely. The latter dogs were able, without the aid of vaso-

constrictor mechanisms, to yield bleeding volumes equivalent to those in the untreated controls.

The improved resistance to the development of irreversible shock is attributed to the absence of prolonged vasoconstriction and its deleterious influence on blood flow to the organs mentioned above.

A study of urinary gonadotropin output in patients with testicular tumor. MONROE J ROMANSKY, EUGENE D ROBIN and LOIS GRAGY (introduced by C E Leese) *Biochemistry Section Laby, Walter Reed General Hospital*. The urinary excretion of gonadotropin was determined in 75 cases of malignant tumors of the testicle. The technique used in this study was a modification of the Heller and Chandler alcohol precipitation method. The hormone extract obtained by this method was injected into 25-40 gram female rats of the Wistar strain. Seventy-two hours after six 1 cc subcutaneous injections of the hormone extract the animals were sacrificed and the ovaries and uteri were dissected free and weighed separately.

The quantity of extract injected into each rat was equivalent to the hormone contained in one tenth of a 24 hour total excretion of urine. This quantity of hormone extract from 17 normal individuals caused no changes in the uteri or ovaries of test rats. An increase of gonadotropin excretion was found in 94 per cent of the patients with tumors. This increase ranged from quantities of hormone sufficient to cause an accumulation of fluid in the uterus (the so-called balloon effect) to quantities of hormone large enough to induce histological changes in the uteri and ovaries of test rats.

We could find no definite correlation between the quantity of hormone excreted and the type of tumor present. In patients where metastasis had occurred there was a tendency for increased gonadotropin excretion but this was by no means a quantitative or constant finding.

Histological studies of the uteri and ovaries of the test animals revealed that both FSH and LH were being excreted. Patients who had undergone removal of one or both testicles in some cases showed a return to normal of gonadotropin excretion. In other cases there was a decrease in the amount of gonadotropin excreted after orchiectomy but the level of excretion remained elevated. This was attributed to increased excretion of FSH due to the removal of the inhibitory effect of the hormone, produced by the testis, upon anterior pituitary secretion.

This study indicates that there is an increased excretion of urinary gonadotropin in malignant tumors of the testes but this increase cannot be used to predict the type of tumor present or the course of the disease.

Relations of anterior thalamic nuclei and mammillothalamic tract to limbic cortex JERZY E. ROSE (by invitation), CLINTON N. WOOLSEY, and LEONARD W. JARUCHO<sup>1</sup> (by invitation) *Dept. of Physiology, Johns Hopkins Univ., School of Medicine, Baltimore 5, Md.* The relations of the anterior thalamic nuclei and the mammillothalamic tract to the limbic cortex were studied in rabbit, cat, and monkey by retrograde degeneration and evoked potential techniques.

Thalamic changes following localized cortical ablations in the rabbit demonstrated that the anteroventral nucleus projects to the anterior limbic region, whereas the anteroventral and anterodorsal nuclei project to the retrosplenial region.

Electrical stimulation of the mammillary bodies in cat and monkey produced potential changes in the limbic cortex. Responses were recorded from area 23 in the monkey and from the retrosplenial region in the cat. Further, under some circumstances the anterior limbic region of the cat was retracted.

These findings, as well as the fact that the anteroventral element is well developed in all mammals and is known to have connections with primate area 23, indicate that the equivalent of area 23 of primates is to be sought within the retrosplenial family of fields in other forms.

Therefore, description of the anterior limbic and retrosplenial fields as distinct regions which develop independently in phylogeny requires modification. It appears that the two regions form a unit consisting of an anterior agranular portion (anterior limbic region) and a posterior granular sector (retrosplenial or posterior limbic region). Since the main known afferent connections to the limbic cortex are from the hypothalamus, and since there is evidence that the anterior limbic region is an autonomic effector area, the suggestion is strong that the limbic cortex constitutes an afferent effector mechanism for autonomic regulation.

Isolation of erythroblasts from the blood of malarial infected ducks H. H. ROSTORFER and R. H. RIGDON (by invitation) *Depts. of Physiology and Pathology, Univ. of Arkansas School of Medicine* White Pekin ducks inoculated with *Plasmodium lophurae* obtained from highly parasitized donor birds develop a profound anemia by the sixth day after inoculation. Birds which survive the infection show a remarkable erythroblast response by the seventh day after inoculation. From sixty ninety per cent of the cells in the blood are erythroblasts which upon centrifugation form a separate layer located above that formed by the normal erythrocytes and the parasitized cells. This layer forms about thirty per cent of the cell volume. It can be quantitatively separated from

the lower layer by repeated washing and centrifugations.

With a sample of 100 ml. of blood containing a high erythroblast count it was possible to obtain a sufficient volume of erythroblasts to carry out determinations of cell volume, color index, oxygen capacity and colorimetric hemoglobin. The color index was approximately one half the normal value for normal erythrocytes. The cell volume index is twice that of normal erythrocytes. The hemoglobin calculated from the oxygen capacity was considerably lower than the colorimetric hemoglobin compared on the basis of the normal relationship in duck blood. This was taken as evidence for the presence of non-functional hemoglobin or hemoglobin like pigment in these cells.

Erythroblasts were suspended in saline and their oxygen utilization determined in the Warburg microrespirometer and compared with that of normal erythrocytes suspended in saline. Erythroblasts were found to utilize approximately five times the amount of oxygen required by normal erythrocytes.

Maintenance of vasodilatation of the extremities of normal persons over a prolonged period after successive meals GRACE M. ROTH and CHARLES SHEARD *Section on Clinical Physiology and Division of Physics and Biophysical Research, Mayo Clinic and Mayo Foundation, Rochester, Minnesota* Since it has been shown by various investigators that there is a significant rise in the cutaneous temperature of the fingers and toes after the ingestion of a substantial meal, and a definite increase in the rate of blood flow (cubic centimeter per minute), the question arose as to whether the rise in cutaneous temperature of the fingers and toes could be maintained for an additional period by the ingestion of three or four successive substantial meals.

Thirty five observations, each involving seven to eight hours, were made of the cutaneous temperatures of the extremities of twenty-four normal persons. For the most part, these persons had low basal metabolic rates and cold feet. In twenty six observations, three successive meals were given, in nine, four successive meals were given, in two, two successive meals were given. In only four instances, with the first meal, was there no rise in the skin temperature of the extremities of those who ingested three meals, and in only one instance was there no significant rise in this temperature with ingestion of the first and second meal, but there was a definite rise after ingestion of the third meal. Two of the same persons who received four meals one day also received three meals on another day, and again there was no significant rise in temperature with the first meal. The effect of sweating on the results will be discussed. In general, a rise in the cutaneous temperature of the extremities could be produced and

<sup>1</sup> Henry Strong Denison Fellow for 1946-47

maintained for a period of seven to eight hours by means of ingestion of successive meals

**The release of ovulating hormone from the hen's pituitary by means of progesterone** IRVING ROTHCILD and R. M. FRAPS, (introduced by Rachmuel Levine) *Bureau of Animal Industry, U S Dept of Agriculture, Beltsville, Maryland* Progesterone induces ovulation in normal hens (Fraps and Dury Proc Soc Exp Biol Med 52 346, 1943) but not in PMS-pretreated hens, and the pituitaries of the latter show a lower ovulating potency than those of normal birds (Fraps, unpublished) This suggested that progesterone acted via the pituitary to induce ovulation, and the following experiment was undertaken to test this possibility Progesterone (10 mg) was injected intravenously into 78 hens approximately 9-14 hours before an expected ovulation Fifty-five were hypophysectomized between 8 and 200 minutes after injection Controls were 8 birds sham hypophysectomized immediately before injection, and 15 birds, injected but unoperated on All birds (15) hypophysectomized between 8 and 106 minutes, 7 out of 8 birds hypophysectomized between 120 and 135 minutes, and 13 out of 32 hypophysectomized between 140 and 200 minutes after injection failed to ovulate All controls except 2 ovulated prematurely Hypophysectomy at equivalent hours in otherwise untreated birds uniformly prevents ovulation (Rothchild Anat Rec 96 #4, 46, 1946)

Follicular atresia in birds failing to ovulate was associated with increase in the interval injection-hypophysectomy, and not with differences in the interval of 10-15 hours between hypophysectomy and autopsy Since injections of subinaximal ovulating doses of pituitary substances induce atresia in hens failing to ovulate (Fraps and Dury Anat Rec 84 #4, 71, 1942) it is probable that atresia indicated incomplete hormone release between injection and hypophysectomy It is concluded that progesterone effects a pituitary ovulating hormone release by a still unknown mechanism

**An instrument to measure muscle tonus in man** I. H. ROZENFELD (by invitation), R. W. GLRARD, L. H. BOYARSKY (by invitation) and J. B. SMYTH (by invitation) *Dept of Physiology, The Univ of Chicago* Despite the introduction of numerous electrical and mechanical instruments, muscle tone is still determined in the clinic overwhelmingly by subjective methods The neurologist feels the hardness of a muscle or the resistance offered to passive stretch This latter is correct in principle and is easily objectified and quantified by a simple instrument

A finger or other desired joint is passively moved through a selected angle, and the tension required for extension (or flexion) is automatically and continuously recorded by a pen A block, carrying a

horizontal steel band spring, is pulled forward by a worm gear in a track The spring, at 90° to the track, carries a lever, parallel to the track, with an ink cup at its end, and from the spring a string passes, also parallel to the track, over appropriate pulleys and ends at a clamp on the finger The hand rests on a wooden form so that the finger is initially flexed at, say, 35° As the block is moved by the worm, the finger is pulled up to a horizontal The pen is moved forward by the block and laterally by the bending of the spring, as tension increases It thus writes on a graph sheet the curve of stretch against tension for the joint and muscle being moved With simple bone measurements and other controls, the tension-length curve of a muscle group can be given in absolute units

Measurements on the flexor digitorum profundus I in normals and patients have shown good constancy of tone for an individual from time to time and between right and left, a range among normal persons within 25%, a heightened tone in fatigued muscle, or with local pain, or after long sleeplessness, a change, up to several hundred per cent up or down, in patients with neurological lesions known to produce spasticity or flaccidity

**A method for the preparation of crystallized oxyhemoglobin** C. H. WILLIAM RUHE (introduced by C. C. Guthrie) *Dept of Physiology and Pharmacology, School of Medicine, Univ of Pittsburgh* Crystallized oxyhemoglobin, which, when used in blood to dye serum, would not alter the volume of the corpuscles, was desired primarily to measure the residual serum in centrifugalized corpuscular sediments The following method was found to be quick, easy and relatively efficient for the preparation of such crystals Defibrinated dog blood is centrifugalized, the serum discarded and the corpuscles washed four times with 0.9% NaCl solution The corpuscles are then laked with twice their volume of distilled water and the corpuscular "ghosts" are removed by centrifugalization The hemoglobin solution is poured into shallow vessels and frozen to a solid mass The frozen mass is chopped or mashed to the consistency of slush and centrifugalization is begun before much melting occurs As the ice crystals melt during centrifugalization, crystals of oxyhemoglobin are freed and rapidly sedimented The supernatant fluid is discarded and the mass of crystals is allowed to dry in evaporating dishes A solution of the freshly prepared crystals shows the absorption spectrum of oxyhemoglobin as determined by the spectroscope and the spectrophotometer The dried mass when ground to a powder has a dark red color The preparation is unstable, as methemoglobin forms on standing

**Effect of morphine and certain other drugs on a sympathetic reaction in man** A. H. RYAN and L. B. NICL *Dept of Physiology and Pharmacology,*

*Chicago Medical School, Chicago, Illinois* Palmar skin resistance (PSR) recorded during a work period of one minute on the bicycle ergometer provides a means of measuring in man a sympathetic nervous response to a uniform stimulus under physiological conditions (Ryan and Ranssen, *A J P* 142 68, 1944) PSR recorded after 55 seconds of work was used as the basis of comparison

Students served as subjects A control record was obtained, the drug given and a second record was obtained after the drug Changes in the response after a drug were compared with changes on placebo A decreased sympathetic response is indicated by a higher PSR at the second observation Between observations subjects were active with their regular laboratory work

Morphine sulfate, 5 or 10 mg subcutaneous, was followed, after 1 hour, in eleven subjects, by a statistically significant decrease in sympathetic response These results support the evidence of sympathetic depression obtained by Himmelsbach (*J P E T* 44 343, 1944)

Oral doses of Amytal 0.10 gram and alcohol 15 cc after 1½ hrs, amphetamine sulfate 10 mg, after 1½ hrs and subcutaneous injection of posterior pituitary solution 6 units, after 1 or 2 hrs, produced no significant change in response Atropine sulfate in sufficient doses was always followed by a decrease of response A subcutaneous injection of 0.8 mg was followed in 1 hr by an average rise of PSR of 75% Three hours after an oral dose of 1.6 mg, PSR was increased by an average of 28% the extremes being zero and 7%

The antithetical ratio for urinary steroids in various pathologic and physiologic conditions WILLIAM T. SALTER, FRANCES D. HUMM (by invitation) and M. JANE OESTERLING (by invitation) *Laby of Pharmacology and Toxicology, Yale Univ School of Medicine, New Haven, Connecticut* Through the application of microchemical methods to relatively small samples of urine, representing three to six hours' excretion, it is possible to determine urinary steroids at short intervals in man and higher animals These may be lumped arbitrarily into three categories, namely, 17 ketosteroids, estrogens and corticoids Of special interest is the ratio of antithetical steroids obtained by dividing 17 ketosteroid excretion (milligrams) into estrogen excretion (micrograms) Although this procedure is a compromise between qualitative accuracy and physiological or clinical utility, the results show significant uniformities in various physiologic and pathologic conditions

The ratio of antithetical steroids between estrogens and 17-ketosteroids is usually under 1.0 for males and usually above 2.5 for adult females in the reproductive age The actual female ratio, however, varies with the menstrual cycle Near menstruation it tends to approach the male ratio,

whereas at ovulation it may reach values of 8 or higher In abnormalities such as hirsutism and infertility, the ratio may be normal even though the absolute values of both classes of steroids are usually high In adrenal virilism in women the steroid ratio is masculine Studies have been made in various conditions including the following virilism, hirsutism, Cushing's syndrome, gynecomastia, prostatism, homosexuality, sterility, eunuchoidism and senility Characteristic ratios for the first five of the conditions are 0.5, 2.4, 0.6, 0.7, 8.5 [*Work aided by grants from the National Cancer Institute Act, Navy Contract N60rr-44, Task Order # VI, and Jane Coffin Childs Memorial Fund*]

Latent period changes in non-propagated responses of normal and novocaine muscles ALEXANDER SANDOW *Washington Square College of Arts and Science* Latency events, recorded with the piezoelectric, cathode-ray method, have been studied in mechanical responses of frog sartori stimulated in a Ringer's bath with square-wave shocks by means of massive (large, plane) electrodes flanking the muscle Normal contractions are unpropagated since a shock excites the whole muscle length simultaneously Threshold shocks, about 0.05 ms duration, cause normal responses with the latency (LR) of the latency relaxation (LR), the depth (R) of the LR, the latency for positive tension (L), and the peak tension all comparable with those of contractions evoked by wire electrode maximum shocks As the strength of the massive electrode shocks is increased, R increases by as much as 300% without appreciable alteration of the other parameters Moderately strong shocks of increasing duration cause pronounced decreases in R and slight reductions in L

Muscles in 0.2% novocaine respond to massive electrode shocks, in general, by producing strong, evidently over all, contractures Although 0.05 ms shocks, only slightly superthreshold for normal muscles, cause no novocaine contractures, increasing the strength and/or the duration of the massive shocks results in twitch like contractures, each preceded by an LR with R up to 30% of that maximally possible in a normal muscle

These results indicate that (1) the latency relaxation is a physiological pie contractile muscular elongation, (2) it is a function of the contractile material, and (3) its behavior is alterable by the electricity of relatively intense, prolonged shocks passing across the muscle during the interval LR

Influence of rate of gastric emptying upon the time of onset of hunger contractions WILLIAM SANCTER (by invitation), M. I. GROSSMAN, and A. C. IVY *From the Depts of Physiology, Northwestern Univ Medical School and Univ of Illinois College of Medicine, Chicago* It has been clearly demonstrated (Ivy, Schmidt, Beazell, *J Nutrition* 12 59, 1936) that liquefaction of a starchy meal by



added malt amylase speeds the rate of evacuation of the meal from the stomach. Addition of amylase accelerates gastric emptying without changing either the volume or the caloric value of the meal. This fact provides a tool with which to investigate the possible relation between rate of gastric evacuation and the length of time after the ingestion of a meal that hunger contractions begin to occur.

In 3 dogs and 1 human subject the length of time between the ingestion of 30 grams of oatmeal cooked in 400 cc of water and the onset of hunger contractions ("onset time") was recorded by the usual balloon-manometer method. In each case at least 20 tests were made, control tests with inactivated diastase were alternated with tests in which active malt amylase was added and the oatmeal was thereby rendered liquid before ingestion. The average "onset times" in the control tests with inactivated diastase were 188, 203, and 160 minutes in the 3 dogs and 134 minutes in the human subject. The corresponding values for the tests in which active amylase was used were 129, 137, 113 and 102. The differences between each pair of average values is statistically significant ( $P \leq 0.05$ ).

These findings indicate that under the circumstances of these experiments, the rate of gastric evacuation is one of the factors which exerts an influence upon the time of onset of hunger contractions.

**Blood volume in the dog determined by Evans Blue and cyanide disappearance.** JACK P. SAUNDERS, RICHARD G. HORTON and RAYMOND E. WESTON (introduced by Harold E. Himwich). *Toxicology Section, Medical Division, Edgewood Arsenal, Maryland*. Following determination of the blood volumes of pentobarbitalized normal dogs with Evans Blue (T1824), the animals were given doses near the LD50 of sodium cyanide solution intravenously. Arterial blood samples withdrawn at various time intervals starting at 5 minutes after injection of the cyanide were analyzed for cyanide content by the method of Aldridge. By plotting the log amount cyanide in the sample against the log time of sampling, there was obtained a straight line for approximately the first 25 minutes which upon extrapolation to  $t = 1$  minute gave an arterial blood cyanide concentration whose relationship to the dose administered was such that calculation of total blood volume approximated the value given by the dye method. No attempt was made to determine the amount of cyanide lost by excretion (i.e. lungs), and it is realized that such loss might not be at a constant rate for the sampling period. For ten dogs the mean per cent blood volume (expressed as per cent body weight) was  $10.2 (s.d. = 1.8, s.e. = 0.57)$  as determined by the dye method, and  $10.8 (s.d. = 2.5, s.e. = 0.80)$  by cyanide disappearance. The mean ratio of cyanide blood volume to the dye blood volume was  $1.05 (s.d. = 0.12, s.e. = 0.038)$ .

**Some factors in ejection of personnel from high speed aircraft.** H. E. SAVELY (by invitation), W. H. AMES (by invitation), H. M. SWEENEY. *Aero Medical Lab., Air Materiel Command, Wright Field, Dayton, Ohio*. The development of high speed aircraft has made it necessary to provide a method of ejecting personnel from aircraft as a means of escape in emergencies.

Studies on an ejection seat test tower have shown that a man can tolerate the force necessary to be ejected upward at a velocity of 60 feet/second with a catapult having a stroke of five feet. Tolerance to ejection is affected by the amount and type of cushioning and the rate at which force is applied. High rates of change of acceleration resulting from a rapid application of force excite a damped oscillation between the man and seat and cause a displacement of the man toward the seat which results in a higher acceleration of the man than is given to a rigid mass equivalent in weight to the man and seat. This increased acceleration on the man can be lowered by reducing the amount of cushion or by using a slower burning powder charge which produces a lower rate of change of acceleration. Accelerations of 20 g's for 0.1 second have been tolerated without ill effects. Present indications are that the 60 feet/second may be obtained with accelerations not exceeding a peak of 15 g's where the rate of change of acceleration does not exceed 200 g's/second.

**Depression of labyrinthine excitability by acoustic stimuli.** N. P. SCALA (by invitation) and E. A. SPIEGEL. *Dept. of Experimental Neurology, Temple Univ. Medical School, Philadelphia, Pa.* In view of the controversial nature of the fiber connections between the acoustic and labyrinthine system, it seemed of interest to ascertain whether an influence of acoustic stimulation upon the vestibulo-ocular reflex arc could be demonstrated. Cats were rotated 10 times in 20 seconds on an electrically driven Bárány chair, on which a bell was placed at a distance of 15 cm. from the animal's head. The bell was rung during the rotation and during the postrotatory nystagmus. A bell with an output of 80 decibels failed to influence significantly the duration of the postrotatory nystagmus and its frequency. However a bell with an output of 110 decibels was able to decrease the duration and the number of beats of the postrotatory nystagmus in one half of the cats tested. This effect outlasted the acoustic stimulation by several minutes. Following a rest period of several hours, the duration and frequency of the postrotatory nystagmus again fell within the range observed before the acoustic stimulation.

**Factors determining the rate of acid excretion by the normal human kidney.** W. A. SCHMIDT (by invitation), J. L. ALER (by invitation), W. D. LOTSPEICH (by invitation), and R. F. PITTS. *Dept.*



of Physiology, Syracuse Univ College of Medicine, Syracuse, New York. The rate of excretion of titratable acid by the normal human subject in ammonium chloride acidosis is low (0.03 milliequivalents per minute) although the urine may be as acid as pH 4.5. The excreted acid is largely monobasic phosphate and to a lesser extent creatinine and organic acid. When one of the three buffers, phosphate, creatinine or p aminohippurate is infused intravenously at such rates as to cause step-wise increases in the rate of excretion, the excretion of titratable acid increases in proportion. Comparisons in a single subject of the relative effectiveness of the three buffers in increasing the elimination of acid indicate that the weakest acid buffer (phosphate) is more effective than the intermediate one (creatinine) and it in turn is more effective than the strongest (p aminohippuric). Within limits the more severe the acidosis, the greater is the rate of acid elimination at any given rate of buffer excretion. Thus, the three factors determining acid elimination by the normal human kidney, (1) rate of buffer excretion, (2)  $pK^*$  of the buffer, and (3) degree of acidosis, are the same as those previously described for the dog (Pitts, R. F., and Lotspeich, W. D., *Amer J Physiol* 147: 481, 1946). The human renal mechanism for the excretion of acid appears to be quantitatively somewhat more effective than that of the dog. [Aided by grants from the John and Mary R. Markle Foundation and the U. S. Public Health Service.]

Accurate analysis of 0.4–0.1 cubic millimeter of gas.<sup>1</sup> BODIL SCHMIDT-NIELSEN (introduced by Laurence Irving) *Edward Martin Biological Lab., Swarthmore College*. The method permits sampling, transfer and determination of respiratory gases in 0.4–0.1 cubic millimeter samples with an accuracy of  $\pm 0.2$  per cent for the larger samples.

The gas is sampled by means of a micro mercury pipette and is stored behind mercury in a glass transfer cup. From this it is drawn into a micrometer burette of approximately 1 cubic millimeter capacity and accurate to approximately one in 3000. The gas sample is extruded into the different absorbing fluids. The gas menisci are located by means of a dissecting microscope. All volumes are read on the micrometer in terms of micrometer units.

Use of one milliliter syringe burette for titrations in the field.<sup>2</sup> KURT SCHMIDT-NIELSEN (introduced by Laurence Irving) *Edward Martin Biological Lab., Swarthmore College*. The present

burette and titration procedure have been developed primarily for field work. Considerable compactness and simplicity have been obtained with but slight sacrifice of accuracy. It is possible with the present burette to perform all ordinary titrations within  $\frac{1}{2}\%$  accuracy.

A 1 cc tuberculin syringe provided with a sealed-on glass tip is used as a burette. The volumes are read directly on the syringe scale. A notch in the plunger engages a spring clip fastened to the syringe barrel and provides an automatic zero point. The spring also gives necessary friction to the plunger.

During the titration the burette is united with the titration vial, and stirring is provided by agitating the whole unit by hand.

A temperature-potassium antagonism observed in luminous bacteria. LEON H. SCHNEIDER (introduced by A. M. Shanes) *Marine Biological Lab., Woods Hole and College of Dentistry, New York Univ.* This investigation was made to determine the effect of potassium upon the intensity of light emission by *Photobacterium phosphoreum*, a psychrophilic luminous bacterial form. For each experiment, the bacteria were suspended in buffered isotonic sodium chloride or sodium and potassium chloride. The predominant effect of potassium was found to depend upon the temperature treatment.

The presence of potassium significantly reduced the irreversible inhibition of luminescence promoted by very high temperatures.

As reported by Johnson and Harvey ('38), potassium reduced the intensity of luminescence at temperatures near the optimum. It is now found that this inhibition increases with a rise in temperature and that this effect of temperature upon the inhibition by potassium is reversible.

At atmospheric pressure and at temperatures below the optimum, potassium chloride (12–36 M) increased the intensity of luminescence as much as 30% above that of a control with no potassium. The application of pressure to the extent of 6000 lb/sq in. at 13°C doubled this activation by potassium.

The data indicate that potassium affects luminescence intensity by acting at more than one locus, the dominant effect in each case being dependent upon the temperature. The protective action of potassium against the action of very high temperatures is due to a slowing by potassium of the irreversible denaturation of one or more enzymes concerned in light emission. The potassium activation of luminescence evident at low temperatures is due to the formation of a catalytically active potassium native enzyme complex and the consequent relative increase in the concentration of active enzyme at the expense of reversibly denatured inactive enzyme.

Accurate analysis of respiratory gases in 0.5

<sup>1</sup> This work was done with the aid of Cost Reimbursement Scientific Research and Development Contract #W33 033 ne 1437S between Swarthmore College (Department of Zoology) and the Air Materiel Command Wright Field.

<sup>2</sup> This work was done with the aid of Cost Reimbursement Scientific Research and Development Contract #W33 033 ac 1493S between Swarthmore College (Department of Zoology) and the Air Materiel Command, Wright Field.

cubic centimeter samples P F SCHOLANDER (introduced by Laurence Irving) *Edward Martin Biological Lab, Swarthmore College* The present analyzer permits the determination of carbon dioxide, oxygen and nitrogen in 0.5 cubic centimeter or less of respiratory gases with an accuracy of  $\pm 0.015$  volume per cent It will handle directly samples containing from zero to over 99 per cent absorbable gases The analysis requires 6 to 8 minutes

A gas sample is introduced into a reaction chamber connected to a micrometer burette and is balanced by means of an indicator drop in a capillary against a compensating chamber Absorbing fluids for carbon dioxide and oxygen can be tilted into the reaction chamber without causing any change in the total liquid content of the system During absorption of gas, mercury is delivered into the reaction chamber from the micrometer burette so as to maintain the balance of the gas against the compensating chamber Volumes are read in terms of micrometer divisions The rinsing fluid and absorbents are accurately adjusted to have the same vapor tension

The role of the mesenteric circulation in the irreversibility of hemorrhagic shock EWALD E SELKURT, ROBERT S ALEXANDER, and MARY B PATTERSON (by invitation) *Dept of Physiology, Western Reserve Medical School, Cleveland, O* The role of vascular pooling in the irreversibility which characterizes hemorrhagic shock is emphasized by the behavior of the mesenteric circulation In animals which die precipitantly, mesenteric vascular resistance continually declines during the hypotensive period, which combined with a relatively elevated portal pressure favors the concept of mesenteric pooling as a feature of final circulatory collapse In more typical cases of better survival, mesenteric resistance increases during the hypotensive period, but a brief period of decline in the average below control follows reinfusion of blood This is believed to represent a critical period of mesenteric pooling, for mesenteric resistance is low combined with adequate arterial inflow, and portal pressure is high, and is marked by a momentary decline of arterial pressure Then a phase of increased mesenteric resistance develops, coincident with which arterial pressure recovers for a time This latter phase of increased vasomotion is probably the result of blood loss through stagnation in the mesenteric vessels, but does not permanently correct for the deficit

To test the hypothesis that initial increase in hepatic vascular resistance in response to hemorrhage may be the initiating factor in the development of mesenteric pooling, portal pressure was experimentally elevated in a group not subjected to hemorrhage This was followed by a decrease in mesenteric resistance and variable decline in

arterial pressure in all Three animals went into circulatory collapse, and at autopsy showed the hemorrhagic intestinal mucosa which characterizes the findings in hemorrhagic shock

Returns of questionnaire concerning biophysics sent to deans and physiologists of American medical schools W A SELLE *Univ of Texas Medical Branch, Galveston*

An attempt has been made to obtain information concerning the teaching of biophysics in the medical schools of this country Questionnaires were sent to the Dean and the Chairman of the Department of Physiology of each of the 68 medical schools

The following questions were asked

- 1 Do you feel that the application of physics to medicine receives sufficient emphasis in medical schools?
- 2 Does it receive sufficient emphasis in your school?
- 3 Are attempts being made now to stress the application of physics in your school?
- 4 If so, what subjects are given special consideration?
- 5 Do you plan to improve instruction in medical physics in your school?
- 6 If you feel that further improvement in the teaching of medical physics is desired, should such instruction be the responsibility of the Department of Physiology, the several pre-clinical and clinical departments concerned, or a special department (Biophysics)?
- 7 Do you believe that biophysics will ever occupy a position in the medical curriculum somewhat similar to that of biochemistry?
- 8 Do you have any suggestions or comments?

The report to be given deals with the returns from this questionnaire

Effect of methyl-testosterone upon the "endocrine kidney" HANS SELYE and HELEN STONE (by invitation) *Inst de Medecine et de Chirurgie Experimentales, Univ de Montreal, Montreal, Canada* The purpose of the work to be reported was to determine whether renotropic steroids cause kidney growth because (due to metabolic effects upon the organism in general) they increase the demand for the excretory function of the organ or whether they exert a true trophic action upon the renal tissue, irrespective of the demand for urine formation

Using our previously described technic for the transformation of the kidney into a purely endocrine organ [Selye and Stone *Journal of Urology* 56:399 (1946)], in a series of albino rats, the hydrostatic blood pressure was sufficiently diminished in the left kidney to stop glomerular filtration without significantly interfering with the nutrition of the organ By injecting varying doses of methyl-testosterone into groups of rats thus pretreated,

it was possible to show that the enlargement of the tubular cells normally caused by this steroid is obvious even in kidneys which do not produce urine

The proximal convoluted tubules, which normally lose their eosinophilia under the influence of the above-mentioned surgical operation, maintain their normal staining properties if adequate doses of testosterone are given

From these experiments, we conclude that the "renotrophic action" of steroids is direct and independent of the filtration and reabsorption phenomena essential for urine formation [*Subsidized by a grant of the Commonwealth Fund*]

The effect of potassium on the injury potential of crab nerve ABRAHAM M SHANES *Bermuda Biological Station, Marine Biological Lab, Woods Hole, Mass and Dept of Physiology, N Y U College of Dentistry* The relation of the "injury" potential to extracellular potassium concentration has been examined in detail for nerves from *Libinia emarginata* and from *Grapsus grapsus* under conditions preventing the swelling which normally occurs in such studies of crab nerve. At potassium levels below that in sea water, potassium is relatively less effective in depressing the potentials than at higher concentrations, and over most of the latter range the potentials are linearly related to the logarithm of the potassium concentration

High concentrations of potassium at the cut end are about as effective as at the intact region in depressing the potentials. With 3 M potassium at the end and 10 mM at the central region a potential difference of about 50 millivolts develops in nerves from *Gecarcinus lateralis*, *Grapsus grapsus*, and *Callinectes ornatus*, Bermuda decapods of widely differing habitats. The potentials of these nerves recover better from strong potassium solutions in which KCl is present in addition to the usual NaCl content than when it replaces an equivalent amount of NaCl. This is in accord with anion permeability as demonstrated in *Libinia*. The recovery is slower than the decline obtained when the strong potassium solutions are first applied. This can be accounted for on the basis of the potential potassium relationship. This relationship also accounts for the smaller decline of potential during anoxia produced by greater concentrations of potassium in the medium [*Aided by grants from the American Philosophical Society and the American Academy of Arts and Sciences and by a fellowship from the Bermuda Biological Station for Research*]

Studies on the effects of vagotomy in rats HARRY SEAY, S A KOMAROV and MARGOT GRUNSTEIN (by invitation) *Fels Research Inst, Temple Univ School of Medicine* Gastric secretion, motility and nutrition were studied in 200 vagotomized rats. The operative approach was subdiaphragmatic,

through a left subcostal incision. The vagi were pulled aborally and approximately 1 cm excised from each, the cranial stump retracting 7 to 10 mm above the diaphragm.

Investigations of immediate effects of vagotomy were confined to interdigestive phase of gastric secretion. This was completely abolished by bilateral vagotomy and reduced approximately to one-half by unilateral section.

Vagotomized animals did not survive on our house diet for more than one week. Autopsy established impaired gastric motility as cause of death. Choline chloride (50 to 100 mg daily/100 grams body weight) increased survival time but in effective dosage was too toxic for prolonged use. Only introduction of predigested protein as a nitrogen source permitted prolongation of the survival. In these "chronic" animals the interdigestive phase of gastric secretion was reduced 80 to 90% in comparison to control animals. Sham feeding produced no gastric secretory response.

The impairment of gastric motility appeared to be permanent. Hail balls (2 cc volume every 4 weeks) developed in the stomach requiring repeated surgical removal.

After bilateral vagotomy the oesophagus dilates to 5 to 10 mm diameter (normal 1.5 to 2 mm), lower third regularly and frequently much higher and at autopsy always contains food.

Digestion and absorption of fat and glycogen storage in liver were not appreciably affected within 4 weeks after bilateral vagotomy.

Studies on absorption through normal human skin WALTER B SHELLEY and FRANK M MELTON (by invitation) *Dept of Dermatology and Syphilology, Univ of Pennsylvania, Medical School, Philadelphia, Penna* Herrmann et al (Science 96:451, 1942) introduced a new type of penetrant vehicle for the transfer of substances into the skin. The present studies demonstrated that vehicles of this type, containing propylene glycol and surface active agents, facilitate the trans epidermal passage of certain pharmacologic agents having a direct and local effect on the human skin.

Following the inunction of acetylcholine chloride and pilocarpine nitrate in these penetrant vehicles, sweating was demonstrated by means of a starch paper iodine method. Atropine sulphate and hyoscine hydrobromide used similarly were effective in inhibiting sweating locally. Epinephrine and histamine phosphate likewise produced local effects. These latter agents proved to be physiological indicators of the route of absorption. The penetration of epinephrine was evidenced by multiple perifollicular areas of blanching which later became confluent. Inunction of histamine resulted in perifollicular wheals, diffuse erythema, and in certain subjects, marked pruritus. These perifollicular effects induced by epinephrine and

histamine indicate that the significant route of penetration is through the folliculosebaceous appendage. This conclusion was further substantiated by the observation that the greatest absorption occurred in the more hairy areas of the body. No evidence of absorption was seen when these drugs, in penetrant vehicles, were applied to the palms and soles, where hair follicles are not normally present.

These pharmacologic agents had to be applied externally in high concentrations to duplicate the effects of extremely low concentrations of the drugs given intracutaneously.

**Effects of low oxygen tension on fertility in adult male guinea pigs.** LANDRUM B. SHETTLER, *Johns Hopkins Hospital, Baltimore 5, Maryland*. Sterility in varying degrees occurs when fowl, cats, rabbits, rams, cattle, and men are transferred from sea-level to high altitude (Monge, *Science*, 95: 79, 1942). Reproductive acclimatization occurs slowly in a population transferred to high altitude, e.g., the first baby was born in Potosi (14,000 ft) 50 years after the city was founded. The capital of Peru was moved from Jauja (13,000 ft) to Lima (sea-level) to lessen sterility.

Male guinea pigs of known fertility were exposed continuously at atmospheric pressure in a gas mixture containing 10 vol %  $O_2$  (19,000 ft) for as long as 89 days. Mating behavior disappeared completely within first week although females in estrus were placed within chamber. Ejaculation produced electrically at weekly intervals showed marked decrease in seminal volume. After 30 days exposure, the semen failed to coagulate. Spermatozoa decreased in number and motility or disappeared completely. After 60 days, numerous abnormal spermatozoa appeared, especially pin-headed, at which time histological studies showed marked degeneration of germinal cells. Weight loss in these animals reached maximum between 30-60 days, after which it remained fairly constant. An equivalent weight loss produced by restriction of food intake of control animals in 20 vol %  $O_2$  showed no effect on fertility.

The 14.5 gram normal hemoglobin increased in all animals until by end of experiment in some this value had doubled.

In the 10%  $O_2$  mixture the experimental males showed little spontaneous activity. When they were put in 20 vol %  $O_2$ , the changes were reversed, and they again proved fertile.

**Presence in blood of a principle which elicits a sustained pressor response in nephrectomized animals.** R. E. SHIPLEY, O. M. HELMER and K. G. KOHLSTÄDT (by invitation), *Lilly Lab for Clinical Research, Indianapolis City Hospital*. A pressor principle has been found in the terminal blood of cats which have died as the result of certain undiagnosed "natural causes,"

DDT poisoning, and prolonged hypotension resulting from the withdrawal of blood.

The pressor principle has not been demonstrated in the blood plasma of bilaterally nephrectomized cats which have died of DDT poisoning, prolonged hypotension or from uremia.

The pressor principle has not been found in the blood plasma obtained from normal living cats or normal cats which had been killed suddenly by various means. It is concluded that a moderately prolonged period of hypotension (with concomitant diminished blood flow and/or blood pressure within the kidneys) is necessary for the production of the pressor principle.

The pressor principle caused a sustained elevation of blood pressure up to 5 hours in cats which were anesthetized, unanesthetized, or pithed, and which had been bilaterally nephrectomized two days before. The injection of the same amount of plasma containing the pressor principle into non-nephrectomized cats did not cause a sustained elevation of blood pressure.

The pressor principle appears to be distinct from renin, angiotonin, pepsitensin, hydroxytyramine, or tyramine because of the difference in the contour of the pressor response, the duration of the pressor response, and the difference in the conditions under which the response is observed.

**The acid-base balance of the blood of aged males.** NATHAN W. SHOCK, *Division of Physiology, National Inst of Health, Bethesda, Md and Baltimore City Hospitals, Baltimore, Md*. Determinations of the acid-base balance of the blood have been made in 40 males between the ages of 75 and 85 years. All the aged subjects were free from clinical sign or previous history of cardiovascular or renal disease. Analyses were made by the Shock-Hastings micro-method on samples of finger blood. This method gives values for pHs, the percentage red cells, the total  $CO_2$  content of the blood, the  $pCO_2$  of arterial blood, and the bicarbonate content of the plasma. Blood samples were drawn from each subject on two different days at approximately one week intervals. Average values were computed and compared with similar determinations made on 100 young adults between the ages of 18 and 25 years. The results showed that the percentage of red cells, the pHs, and the bicarbonate content of the serum was significantly lower while the  $pCO_2$  was higher in the aged subjects than in young adults. Many of the aged subjects showed signs of a slight metabolic acidosis, and some showed a superimposed respiratory acidosis.

**Hepato-renal factors in circulatory homeostasis.** XII Alterations in renal vaso-excitor mechanisms during experimental hypertension. EPHRAIM SHORR, B. W. ZWEIFACH, R. F. FURCHGOTT (by invitation) and S. BAEZ (by invitation), *Dept of Medicine, Cornell Univ Medical College and The*

*New York Hospital, New York City* Kidney slices from normal dogs produce a vaso excitor principle (VEM) on *in vitro* incubation, only under anaerobic conditions, under aerobic conditions, they inactivate VEM. This represents a type of Pasteur reaction analogous to the restriction of glycolysis in normal tissues to anaerobiosis. The renal mechanisms regulating VEM formation undergo significant alterations following partial constriction of the renal artery by a Goldblatt clamp and the induction of hypertension.

Within 48 hours, the kidney is transformed into an organ which elaborates VEM continuously even on aerobic incubation, a situation comparable to the derangement of the glycolytic mechanism in cancer cells. Studies of clamped kidneys, removed at various stages in the hypertensive syndrome, show a persistence of this metabolic defect even in animals with only one kidney clamped and whose blood pressure has returned to normal. Such kidneys also exhibit a progressive impairment of their capacity to inactivate renal VEM on oxidative incubation *in vitro*. The same derangements are present in dogs with a malignant type of hypertension which has persisted despite removal of renal clamps, the kidney, after removal of the clamps, continuing to form VEM aerobically. On the other hand, when clamping is associated with renal damage and failure to develop sustained hypertension, *in vitro* studies indicate that the clamped kidneys have lost their capacity to form VEM, both anaerobically and aerobically.

The basis for the aerobic production of VEM by clamped kidneys of hypertensive dogs is believed to reside in the loss of the renal mechanism for the inactivation of VEM. [Aided by grants from the Josiah Macy, Jr. Foundation and the Eli Lilly Co.]

The role of potassium in conduction of the impulse in striated muscle. F. J. SICHEL and CHERYL PARKHURST (by invitation) *Univ. of Vermont College of Medicine*. It has been previously shown that non conducted, graded contractile responses to electrical stimulation may be obtained from the frog isolated skeletal muscle fibre preparation with cut ends. Also, similar behavior may be elicited from intact entire muscles if they are bathed in a medium containing three to four times the usual concentration of potassium ion. The present experiments were undertaken to decide whether these effects were due in each case to an altered gradient of potassium ion concentration. If this were the case the potassium ions must diffuse out of fibres with cut ends and accumulate in the medium sufficiently rapidly to abolish conduction within a few minutes.

The sartorius muscles of frogs were carefully dissected out, rinsed quickly in Ringer's solution, lightly blotted on filter paper, and weighed. They were then placed in 31 ml. of Ringer's solution per

gram muscle. Some of these preparations were kept as controls. In others the muscles were traumatized by cutting each transversely into three fairly equal parts. In all cases the potassium ion concentration of the medium was determined with a flame photometer after the preparations had been shaken for periods varying from one minute to twenty-four hours.

It was found that the rate at which potassium left the cells and accumulated in the medium was of the order of magnitude which could explain the failure to conduct in a time of the order of minutes. Further experiments are being carried out to determine this rate with different volumes of the medium, and also, if possible, to determine whether in the injured cell the outward diffusion is solely through the cut ends, or whether the entire surface of the fibres has been made more permeable to the potassium ion. [Supported by a grant from the Penrose Fund of the American Philosophical Society.]

Bronchodilator action of some N-alkyl analogues of epinephrine. O. H. SIEGMUND (by invitation), H. R. GRANGER (by invitation) and A. M. LANDS. *Pharmacological Research Lab., Frederick Stearns and Co., Division of Sterling Drug Inc., Detroit, Michigan*. Several analogues of the primary amine of 1-(3',4'-dihydroxyphenyl) 2-aminoethanol, the N-methyl-, (epinephrine), the N-ethyl- and the N-isopropylamine as the HCl salts were investigated to determine their antiasthmatic efficiency and to correlate roughly, structure with activity.

Guinea pigs whose control reaction times to histamine-induced asthma were known, were treated with two dose levels of each compound (0.25 mg./kg. and 0.1 mg./kg.), and histamine asthma was again induced. Reaction times were recorded and compared directly. The primary amine was the least effective causing little increase over normal reaction time at 0.25 mg./kg., but causing approximately double the control time at 0.1 mg./kg. The N-methyl-, -ethyl, and -isopropyl analogues were relatively close in activity at 0.25 mg./kg., but showed a marked increase in reaction time at the 0.1 mg./kg. dose, the increase being proportional to the size of the N-alkyl group. The control time for the onset of asthmatic symptoms was 0.78 minutes. At 0.10 mg./kg., the following reaction times were observed, primary amine—1.75 min., N-methyl—3.38 min., N-ethyl—3.78 min., and isopropylamine—4.91 minutes. The N-isopropyl analogue was tested at 0.15 mg./kg. and 0.20 mg./kg., giving 5.26 min. to more than 6.00 minutes respectively, for the onset of asthmatic symptoms. All treated animals resisting asthma for over 6 minutes were arbitrarily considered fully protected.

Lung perfusion experiments with histamine-

duced bronchial constriction corroborated the above data, indicating strongly that the N-isopropyl analogue of epinephrine is the most efficient bronchodilator yet studied in this series

Acute toxicity was determined by injection into albino mice. The approximate LD50 for 1-epinephrine HCl was found to be 40 mg/kg. The approximate LD50 of related compounds was found to be as follows: the primary amine (nor-epinephrine) 10 mg/kg, N-ethyl analogue 20 mg/kg, N-isopropyl analogue 460 mg/kg.

**Visual fatigue.** ERNEST SIMONSON, JOSEF BROZEK (by invitation), and ANCEL KEYS *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis*. The visual task consists in the recognition of letters, which are presented in random order on a belt moving behind a narrow slit. The letters, printed on small strips of paper, are mounted on a rubber belt driven by a synchronous motor with variable reduction gears. Lamps are mounted in metal boxes shielded from the subjects, and the illumination level is adjusted by means of diaphragms in front of the lamps. The subjects are seated in individual booths. Three different types of lamps (Frosted, Verd-A-Ray, Natural White) were used at various levels of illumination. The letters were copied down by hand on a roll of paper, led beneath a metal plate containing a small window, and wound up by the subject by pressing a lever. The writing of the letters and the transport of the paper was done without visual control. Neither operation requires any appreciable manual skills. Work samples of 200 letters were used for evaluation of the performance. Various visual functions were tested before and after two hours of work. The methods for the measurement of visual acuity, fusion frequency of flicker, abduction and adduction power, convergence and accommodation near point, eye movements by means of the ophthalmograph and brightness discrimination are demonstrated. [This work was supported by the Verd-A-Ray Corp., Toledo (Ohio)]

**Energy cost in horizontal and grade walking of poliomyelitis patients.** ERNEST SIMONSON and ANCEL KEYS *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis*. The energy expenditures of two poliomyelitis patients, one clinically completely recovered from paralysis (EB), the other one with an almost atrophic right leg (JD) were compared to those of two normal subjects during walking on a treadmill at 2, 2.5, 3.0, 3.5 and 4.0 m p h and 0, 5%, 7.5% and 10% grade. EB's energy expenditure expressed as excess Cal per m distance per kg body weight coincided with the normal values at all variations of speed and grade up to 3.5 m p h with a slight tendency to higher values at 4.0 m p h. However, EB was not able to maintain a steady state at 3.5 m p h, 7.5% and 10% grade, and 4 m p h at all grades. Normal

subjects maintain a steady state at least up to 30 minutes at these variations. JD's energy expenditure with braces exceeded the normal values (1.5 and 2.6 times) at all variations investigated (up to 3 m p h), but, surprisingly enough, the relative increase was higher in horizontal than in grade walking, a part of the energy waste in horizontal walking can be utilized for climbing. Without braces JD's excess energy expenditure was considerably higher. The respiratory efficiency (cc oxygen consumption per 100 cc pulmonary ventilation) of JD was definitely below normal at all variations. The respiratory efficiency in both JD and EB showed a pronounced drop at the higher speeds and grades, this phenomenon resembles the fatigue effect in hard muscular exercise. [This work was supported by a grant from the National Foundation of Infantile paralysis]

**Effect of three types of illuminants on visual performance and fatigue.** ERNEST SIMONSON, JOSEF BROZEK (by invitation) and ANCEL KEYS *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis*. The work task involved recognition of letters (size of 1 minute visual angle, exposure time 0.56 seconds). The visual performance was evaluated in terms of correctly recognized letters per 200 letters, at the beginning, middle and end of the 2-hour visual work period. Duplicate experiments were performed with each illuminant—ordinary inside frosted lamps (Fr), "natural white" (NW) and "Verd-A-Ray" (VR). On each day all 3 illuminants were used, 2 subjects working with each lamp. The subject pairs and illuminants were rotated for consecutive experiments. The average performance scores, each based on 12 observations, were 164.8, 166.1 and 171.3 for Fr, NW and VR respectively with a statistically significant difference between Fr and VR (F-test). There was a statistically highly significant performance drop in all illuminants from the start to the end (Fr—13.17, NW—15.25, VR—13.75). The average difference between maximum and minimum performance, characterizing the variability of an individual's performance within a work session, was 25.9, 24.9 and 16.8 for Fr, NW and VR, the superiority of VR being statistically significant. The fusion frequency of flicker, tested together with other functions before and after the performance, dropped -1.00, -1.42 and -0.36 for Fr, NW and VR, the difference between VR and NW approaching statistical significance. The recognition time for threshold-size dots increased 1.54 sec (VR), 3.50 sec (Fr) and 6.04 sec (NW). The difference between VR and NW was statistically significant. [This work was supported by the Verd-A-Ray Corp., Toledo, Ohio]

**The oxidation of certain amino acids and proteins by peroxidase and hydrogen peroxide.** IRWIN W. SIZER *Dept of Biology, Massachusetts Inst of*

*Technology* Crude and crystalline peroxidase prepared from horse radish were used in the study of the oxidation of amino acids and proteins by hydrogen peroxide. The reaction was investigated by determining the residual  $H_2O_2$  as indicated by manometric measurements of oxygen liberated at the end of the reaction after adding the catalyst,  $MnO_2$ . Of all the amino acids studied only tyrosine, tryptophane, lysine and possibly cystine were oxidized by peroxidase- $H_2O_2$  at pH 7.3 and at 37° C. Both the oxidized tyrosine and tryptophane were colored, absorbing strongly in the blue violet, the former also displayed a marked increase in absorption in the ultraviolet, when compared with a suitable control, and showed a decrease in color when tested with Millon's reagent for tyrosine.

From the manometric studies it was concluded that of the many proteins investigated only the following were oxidized by  $H_2O_2$  in the presence of peroxidase: pepsin, trypsin, chymotrypsin, bovine fibrinogen, casein, mucin and soy bean proteins. All the oxidized proteins except the last showed a greatly increased absorption in the ultraviolet, and, in addition, the proteases also became colored, absorbing strongly in the blue-violet. The great similarity between the effects of peroxidase  $H_2O_2$  on tyrosine and susceptible proteins strongly suggests that in these proteins it is the tyrosine moiety which is oxidized. These results are similar to those previously reported for the action of tyrosinase on proteins.

After treatment with peroxidase  $H_2O_2$  the proteases had the same residual enzyme activity as when treated with inactivated peroxidase- $H_2O_2$ .

The role of the pericardium in acute cardiac dilatation. IRWIN H. SLATER and HARRY F. WEISBERG (introduced by Richard C. de Bodo). *Dept. of Pharmacology, New York Univ. College of Medicine, New York*. It has been suggested that the inelastic fibrous structure of the pericardium prevents acute dilatation of the heart to any significant degree.

In a series of experiments on anesthetized dogs ventricular volume was recorded directly with the Henderson cardiometer. The pericardium was separated from its diaphragmatic attachment and cleaned. Determinations were made before and after removing the entire pericardium. Mean arterial and venous pressures were also recorded. Acute cardiac dilatation was produced by the following agents: sodium citrate sodium thiosulfate, potassium chloride, sodium pentobarbital and chloroform.

The dogs ranged between 12.7 and 17.3 kg and the heart weights between 108 and 144 grams. With the pericardium intact an increase in volume of the two ventricles up to 40 cc was observed. Such dilatations were associated with a definite rise in

venous pressure. The change in arterial pressure varied with the different agents.

After the pericardium had been removed, a somewhat greater degree of dilatation was recorded with only a slight rise in venous pressure. The arterial pressure changes did not differ markedly from those noted in the experiments with the pericardium intact.

The ventricular dilatation recorded by this cardiometric technique will be correlated with roentgenographic measurements.

**Plethysmographic study of leg volume changes in man during positive acceleration on a centrifuge.** O. L. SLAUGHTER (by invitation) and E. H. LAMBERT. *Acceleration Lab. and Section on Physiology, Mayo Foundation, Rochester, Minnesota*. Plethysmography was used to determine to what extent pooling of blood occurs in the lower leg of subjects in a sitting position (heels 7 inches below buttocks) during exposures to positive acceleration which cause impairment or loss of vision. Observations were made on fifteen men during 218 exposures to acceleration in a comfortable environment (average, 71°F, 51 per cent relative humidity). Accelerations were attained within 3 seconds after 1.5 g was exceeded and were maintained for 15 seconds.

Displacement of air from the plethysmograph was due to leg sinking into the plethysmograph as well as to an increase in leg volume during acceleration. Corrections for changes in position of the leg were made from exposures to acceleration in which a cuff about the thigh was inflated to arterial occlusive pressures.

During 15 seconds at accelerations of 2.5, 3.0, 3.5 and 4.0 g the increase in leg volume averaged 31, 34, 40 and 42 cc, respectively (standard deviations, 7.1, 8.6, 9.8 and 8.2). This was 1.3 cc per 100 cc of leg tissue at the average blackout threshold (37 g). Compensatory recovery of arterial blood pressure began after 5 seconds and recovery of vision after 10 seconds' exposure to acceleration, although the increase in leg volume continued for 45 to 60 seconds, if acceleration was continued. The increase in volume of the lower leg was more closely correlated with the magnitude of acceleration than with the severity of symptoms which an individual experienced. No correlation was demonstrated between increase of leg volume and g tolerance of individuals.

The use of jejunal transplants in the construction of ante-thoracic esophagus. JOHN W. SLOAN and JOHN VAN PROHASKA (introduced by G. E. Wackerlin). *Dept. of Surgery, Univ. of Illinois, College of Medicine*. Even though the operation of transthoracic gastro-esophagostomy has reached a considerable perfection and safety, there remains a number of instances in which the continuity of



the act of swallowing can be accomplished only by the construction of an ante-thoracic esophagus

Skin tubes used for the construction of such an esophagus were found to be unsatisfactory because of the formation of fistulae, the growth of hair within the tube, and strictures at points of anastomoses. In order to overcome this difficulty, a segment of jejunum, with its blood supply intact insofar as possible, was dislocated and brought up through a subcutaneous channel. At a second stage, the distal end of the jejunum was anastomosed to the stomach and the proximal end to the stump of the cervical esophagus. Satisfactory results were obtained in four patients.

The experimental work on animals showed that strictures of the transplanted jejunum would occur if the segment of jejunum was deficient in blood supply.

**Respiratory responses resulting from temporary pulmonary artery occlusion in the intact unanesthetized dog.** DONN L. SMITH<sup>1</sup> (by invitation), ROBERT F. RUSK (by invitation) and CLARENCE A. MAASKE. *The Dept. of Physiology and Pharmacology, Univ. of Colorado School of Medicine, Denver.* A technique has been developed for occluding the pulmonary artery in the intact, unanesthetized dog. An adjustable plastic clamp of triple-screw design is positioned around the root of the pulmonary artery during aseptic surgery. A collar, which guides the shaft of the clamp, is anchored subcutaneously on the chest wall. A small stylette, inserted through the skin and fitted to the grooved end of the shaft, is used to produce the desired degree of occlusion.

Respiration is recorded by means of a pneumograph, while the partially-trained animals are lying quietly on their right sides. The skin over the head of the clamp shaft and collar is infiltrated with procaine prior to manipulation.

As the degree of occlusion of the pulmonary artery approximates 75-80 per cent, there is an immediate and marked increase of respiratory amplitude and often a coincident increase of rate. Release of the constriction promptly reestablishes normal respiratory rhythm.

Pulmonary artery occlusions are attempted as early as 72 hours following placement of the clamp. Studies on venous and arterial blood pressure changes during occlusion will be presented.

**Some toxic effects of thiamine.** JAY A. SMITH (by invitation), PIERO P. FOA, and HARRIET R. WEINSTEIN (by invitation). *Dept. of Physiology, Chicago Medical School, 710 S. Wolcott Avenue, Chicago, Illinois.* Twelve dogs, anesthetized with ether, received thiamine intravenously, with and without artificial respiration. Blood pressure from the central and the peripheral end of the femoral artery, respiration, and the electrocardiogram were

recorded. Blood samples were taken from six animals and analyzed for free thiamine.

When artificial respiration was used, doses up to 125 mg./kg. resulting in concentrations up to 36.9 mg./100 cc. blood, were tolerated. No larger doses were tried. On the other hand, without artificial respiration, doses resulting in concentrations of only 7.2-10.0 mg./100 cc. blood were invariably fatal. Thus the principal action of thiamine in toxic doses is respiratory paralysis, its effectiveness is reduced by artificial respiration.

The largest doses of thiamine caused a temporary fall in blood pressure of 19-91 mm. mercury when artificial respiration was used. When artificial respiration was not used, the fall was followed by partial recovery, then by an inevitable fall to zero. Simultaneous with the partial recovery and final fall, there was an increase in the voltage of the T-wave, these phenomena are probably due to anoxia.

Both central and peripheral blood pressures decreased. The latter remained low longer than the former, indicating that thiamine causes vasodilation. These results were not affected by vagotomy and atropinization.

The heart itself seems to be affected because even during artificial respiration, large doses of thiamine decreased the voltage of the QRS complex. Also, the contractions of the isolated turtle heart perfused with 25 mg. thiamine/100 cc. Ringer's at pH 7, decreased in amplitude and frequency. Larger doses caused incoordination and standstill. [This work was made possible by a grant from the John and Mary R. Markle Foundation.]

**Lack of effect of a digitalis preparation<sup>1</sup> on the blood pressure decrease caused by aminophyllin.** JAY A. SMITH (introduced by L. B. Nice). *Dept. of Physiology and Pharmacology, Chicago Medical School, 710 S. Wolcott Avenue, Chicago, Illinois.* Alterations in the effect of aminophyllin by digitalis preparations was sought, since these drugs are commonly used together.

Blood pressure, respiration, and the electrocardiogram were recorded on 18 dogs anesthetized with ether. Aminophyllin (0.1, 0.2, and 0.4 cc.) and Cedilanid (0.5 cc./kg.) were given by rapid intravenous injection. These doses of aminophyllin caused measurable decreases in blood pressure, and this quantity of Cedilanid caused a depressed ST-segment and, occasionally, extrasystoles. Aminophyllin was injected before and at least 30 minutes after Cedilanid.

The table shows that as the dose of aminophyllin was increased, the fall in blood pressure increased and that the resulting fall was similar both before and after Cedilanid.

In other experiments, larger doses of amino-

<sup>1</sup> Life Insurance Medical Research Fellow

<sup>1</sup> Cedilanid, Sandoz Chemical Works, Inc. New York. All drugs were supplied by the Sandoz Company.



phyllin, injected intramuscularly, gave similar results

Thus the fall in blood pressure caused by aminophyllin is not altered by Cedilanid

Cedilanid (cc /kg )	Aminophyllin	
	Dose (cc )	Blood pressure fall (mm Hg)
0.0	0.1	6.4
0.5	0.1	7.0
0.0	0.2	9.7
0.5	0.2	9.2
0.0	0.4	13.8
0.5	0.4	14.5

Studies on the biological exchange of radio-antimony in animals and man<sup>1</sup> ROBERT E. SMITH (introduced by B. G. King) *National Naval Medical Center, Naval Medical Research Institute* The radioactive isotopes of antimony,  $^{122}\text{Sb}$ , and  $^{125}\text{Sb}$ , with half lives 28 and 60 days, respectively, have been used by the radiobiology group at the Naval Medical Research Institute and Department of Terrestrial Magnetism, CIW, in tracer studies on the exchange and tissue distribution of antimony administered in sublethal dosage to chicks and guinea pigs as stibine gas ( $\text{SbH}_3$ ) and as tartar emetic to hamsters (both normal and infected with *Schistosoma mansoni*), rabbits and human patients. By Geiger counter measurements of appropriate samples, the concentration of antimony was determined as a function of time following a single dose for various tissues as well as blood and excretion products.

With both compounds studied the antimony was rapidly removed from the blood stream, but the red cell/plasma antimony ratio in stibine treated animals remained between 10 and 50 while a ratio approaching unity was obtained with tartar emetic. Of the organ systems studied, the highest concentration was obtained in the liver, spleen and kidney, in decreasing order, but with the thyroid frequently exceeding the spleen. In the hamsters infected with *Schistosoma*, the adult flukes in the blood stream were found to contain antimony in concentration about equal to that of the spleen. Other tissues such as lung, muscle, heart and brain were progressively lower than spleen but greater than the plasma level.

Excretion of antimony proceeds via the bile and kidney and for the body as a whole was calculated to be about five times more rapid in the stibine treated guinea pigs (50 per cent excretion time

about one hour) than in the chick. Total excretion studies on two human patients each given a single dose (0.8 mg/kg body weight) of tartar emetic indicated the 50 per cent excretion time to be of the order of 500 hours for humans.

The differential action of erythroidine in the normal and in the decerebrate animal<sup>1</sup> WILBUR K. SMITH *Dept. of Anatomy, The Univ. of Rochester, School of Medicine and Dentistry, Rochester, New York* Two erythroidine compounds, dihydro-beta-erythroidine hydrobromide and beta erythroidine hydrochloride were studied to determine whether or not they exerted any selective action on neuromuscular mechanisms. In the intact non anesthetized cat and monkey, the administration of appropriate doses of either of these alkaloids was found to produce a gradual relaxation of muscle tension without abolishing either muscular movements or tendon reflexes. Larger amounts resulted in the abolition of extremity movements without loss of tendon reflexes and with retention of respiratory movements. A considerable increase in the amount is necessary to abolish respiration. Under these conditions there is no significant alteration in arterial pressure or cardiac rate and under artificial respiration the animals returned to normal. The intravenous injection of prostigmine abolished the effects of the erythroidine almost immediately.

In decerebrate preparations administration of either compound caused a gradual and complete relaxation of the rigid extremities with retention of the tendon reflexes and without impairment of respiratory movements. Larger amounts abolished the latter. Recovery under artificial respiration ensued promptly upon the discontinuance of the erythroidine or upon administration of prostigmine, and rigidity returned.

The mechanism of the differential action of these erythroidine compounds in diminishing muscle tension without abolition of tendon reflexes, movements of the extremities or respiratory movements is in process of investigation. The properties of these compounds in reducing muscle tension suggest their possible usefulness in certain types of neuromuscular disorders in man. [Aided by a grant from the National Foundation for Infantile Paralysis, Inc.]

The relation of cytoarchitecture to response elicited by electrical excitation of the cerebral cortex WILBUR K. SMITH *Dept. of Anatomy, The Univ. of Rochester, School of Medicine and Dentistry, Rochester, New York* Excitation of the cortex forming the rostral part of the cingular gyrus in the monkey (*Macaca mulatta*) produces a number of widely divergent responses including vocalization, slowing or temporary cessation of respiratory

<sup>1</sup> The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

<sup>1</sup> The erythroidine compounds were kindly furnished by Merck and Company Rahway, New Jersey.

movements, inhibition of extremity movements and relaxation of muscular tension, alterations in the cardiovascular realm, and piloerection. The responsive field lies mostly within, but appears not to include all of the region which Brodmann designated as area 24 in his map of *Cercopithecus*. Study of the cytoarchitecture of the responsive cortex discloses that it does not constitute a uniform cytoarchitectural field, but shows a wide variation in its different parts. Furthermore, it has not been possible to correlate the response elicited with any specific cytoarchitecture within this field. Responses apparently identical with those elicited from the cingular cortex have been obtained from cortical areas differing widely in their cytoarchitecture, and also from subcortical structures.

On the basis of these findings, it seems necessary to re-examine critically the evidence upon which has been built the concept of a specific relation between so-called cytoarchitectural areas and function. Our investigations thus far indicate that the responses elicited from the cerebral cortex upon electrical excitation depend more, if not entirely, upon the connections of the responsive focus with lower levels than upon cytoarchitecture. [*Aided by a grant from the John and Mary R. Markle Foundation*]

**The relationship between protein and the sulfur-containing amino acids in protection against methyl chloride poisoning.** WILLIE W. SMITH, *Industrial Hygiene Research Lab., National Inst. of Health, Bethesda, Maryland*. Rats exposed to methyl chloride 2,000 p.p.m. 6 hours a day 6 days a week survive equally long on diets ranging from 4 to 20 per cent casein. Possibly maintenance requirements are so graded that essentially no sulfur-containing amino acid is available for detoxication. Addition of cystine or methionine results in protection averaging 12.6 days per meq. supplementary sulfur per 100 grams diet.

Casein above 20 per cent does not increase pre-exposure growth, consequently dietary amino acids are present in excess. Survival time becomes somewhat longer, but in no case reaches that anticipated from the increase in amino acid sulfur. Rats on 47 per cent casein compared with litter-mates on 20 per cent casein supplemented by cystine and methionine to the level of 47 per cent casein have equal growth rate and sulfur intake, but the extra casein is only about a fourth as effective in protecting against death as is the equivalent sulfur-containing amino acid. At the higher casein levels supplementary methionine provides protection for only 1.5 to 5 days per meq. per 100 grams. The casein effect in these experiments cannot be attributed to higher maintenance requirements. The possibility of amino acid competition for a common enzyme system is being investigated.

Exposed rats on certain diets well supplemented with cystine and methionine may grow for several

months at a rate comparable to unexposed controls, losing weight only during the few days immediately preceding death. Such observations indicate a more complex relationship between organism, toxic agent, and protective agent than is sometimes postulated.

**The response of the gall bladder to various stimuli before and after vagotomy.** W. J. SNAPE (introduced by J. E. Thomas), *Dept. of Physiology, Jefferson Medical College, Philadelphia, Pennsylvania*. The common bile duct was temporarily cannulated through a permanent duodenal fistula. Over two hundred experiments were performed on six dogs. Intubation of the duct by means of a glass catheter, which rendered the terminal sphincter incompetent, did not result in a flow of bile. We interpret this to mean that retention of bile in the gall bladder is not dependent on closure of the biliary orifice by the action of the sphincter. The latent period for the gall bladder contraction after duodenal instillation of cream, fatty acids, casein, skimmed milk and peptone, as well as the volume of bile expelled was compared before and after vagotomy. Vagotomy while not abolishing the capacity of the vesical to contract did prolong the latent period and otherwise modify the response. Control observations were made with cholecystokinin given intravenously. Latent periods and other features of the response to cholecystokinin were not modified by vagotomy.

**The effect of various stimulant drugs on dogs made apneic by anoxia.** FORREST E. SNAPP (by invitation), JOHN H. IVY (by invitation) and HARRY F. ADLER. While much work has been reported in the literature on the effect of various respiratory stimulants on human beings and animals depressed by anesthetic agents, comparatively little has been done on the effect of such drugs on animals made apneic by anoxia. It was thought worthwhile to investigate this latter problem to determine whether the respiratory mechanism depressed by anoxia is capable of stimulation by drugs. The problem is of additional interest because of the wide use of such stimulants on patients who have been asphyxiated and on newborn infants who are suffering from acute anoxia.

Our experiments were carried out on dogs lightly anesthetized with nembutal. Blood pressure, respiratory depth, rate and minute volume were recorded and blood oxygen and hemoglobin levels were determined. The animals were given 100% nitrogen to breathe until apnea occurred after which the stimulant drug was administered intravenously. The following drugs were tested: coramine, alphalobeline, amphetamine, metrazol and caffeine. One series of dogs was given intravenous glucose to determine if this might aid the animal in withstanding the anoxia by prolonging the period before apnea.

In the dosages used the drugs only infrequently

caused spontaneous resumption of respiration although the animals were easily revived by means of artificial respiration using 100% oxygen

A suppressor cerebello-bulbo-reticular pathway from anterior lobe and paramedian lobules R S SNIDER (by invitation), H W MAGOUN and W S McCULLOCH *Dept of Psychiatry, Univ of Illinois College of Medicine and the Dept of Anatomy, Northwestern Univ School of Medicine* In cats and monkeys excitation of (1) the tactile projection areas of cerebellar cortex (near vermal vein of anterior lobe and anterior folia of paramedian lobule), of (2) fastigial nucleus, of (3) bulbar reticular formation or of (4) its descending fibers in the angle of the pyramidal decussation suppresses motor response to cortical stimulation, diminishes tendon reflexes and relaxes decorticate or decerebrate rigidity With electrical recording, impulses from the first structure reach the third after three milliseconds, whereas those from the second, after approximately one millisecond This system is predominantly ipsilateral in its action

Deep reflexes and tonus are enhanced by destruction of the enumerated structures, each of which is necessary for the aforesaid functions of all above it The suppressor action of the fastigial nucleus is not maintained in the absence of the cerebellar cortex, nor is that of the bulbar reticular formation in the absence of cerebellar and cerebral projections to it

Hence, from Purkinje cells of cortex of anterior lobe and paramedian lobule of cerebellum, impulses pass to the fastigial nucleus whence they are relayed to the bulbar reticular suppressor mechanism and thence, relayed by cells whose axones pass through the pyramidal angle down the ventrolateral fasciculi of the cord, prevent response of anterior horn cells to cortical, tonic and reflex excitation [Aided by a grant from The Rockefeller Foundation]

The oxygen concentration in the blood of breathing fetuses FRANKLIN F SNIDER *Harvard Medical School* The development of a technique by which fetuses showing rhythmical respiratory movements can be kept under direct observation for several hours within the unopened uterus makes possible the determination of the state of oxygenation of the blood at a high level of fetal activity The results showed beyond doubt that fetal respiration was occurring in the presence of a high oxygen level in the blood, rather than being caused by deep asphyxia In fact, measurements revealed that the normal oxygen concentration is considerably higher than that commonly reported heretofore

In blood of the umbilical vein obtained promptly following the escape of the breathing fetuses from the uterus into the saline bath, while the circulation through the cord was maintained, the oxygen content averaged 13 volumes per cent in a series of 44 fetuses of 19 litters of rabbits, which included

19 previsible, 8 premature, and 17 fullterm fetuses The oxygen saturation was over 90 per cent in the blood obtained from previsible and premature fetuses, and averaged 78 per cent in fullterm fetuses at 32 days The carbon dioxide content averaged 42 volumes per cent in the series Even before interference with the cord circulation such as that entailed in venapuncture, the bright red color of the blood in the umbilical vein while the umbilical arteries were blue, indicated that the oxygen concentration was higher than that currently described in the literature [Supported by a grant from the John and Mary R Markle Foundation]

Blood pressure in seasickness A SOKALCHUK (introduced by E A Spiegel) *Temple Univ Medical School, Philadelphia, Pa* Experimental studies (Spiegel and Démétrades, *Arch ges Physiol* 196 185, 1922) demonstrated that all types of labyrinthine stimulation induce a fall or multiphase change of blood pressure In seasickness, anemia of the eyeground (Kramer, *Prag med Wchnschr* 17 465, 1892) was observed, while Hemingway (*Fed Proc* 4 33, 1945) denied significant changes of blood pressure in motion sickness produced by 20 minutes swing It may therefore be of interest to report blood pressure readings in seasick crew members of a destroyer subjected to a combination of rolling, pitching, yawing and up and down motion for hours and days An average of 6% of the men became seasick In 37 men systolic and diastolic blood pressure were repeatedly measured in port and during seasickness

	Rise (mm Hg)		Fall (mm Hg)						Fall or rise
	11-15	1-10	1-10	11-15	16-20	21-25	26-30		
Av syst		2	15	8	4	2	1	(+4 to -11)	
Max syst	1	1	11	6	3	3	2	5	
Av diast		0	16	4	5	2		(+11 to -13)	
Max diast	1	5	11	7	5		4	4	

Rise as well as fall of the systolic pressure (average plus 4 to minus 11) appeared in 5 cases Fall of the systolic pressure of 1-10 mm was much more frequent (15 cases) than a corresponding rise (2 cases) 15 men (40%) showed an average fall of 11-27 mm, 13 (35%) a maximal fall above 15 mm The reaction of the diastolic pressure was somewhat similar (see table)

Interrelation between anterior lobe of the cerebellum and the motor area V SORIANO (by invitation) and J F FULTON *Laby of Physiology, Yale Univ School of Medicine, New Haven, Conn* In the rhesus macaque, unlike dog and cat, complete ablation of the anterior lobe of the cerebellum fails to cause marked augmentation of the positive supporting reactions with spasticity If, however,

ablation of the anterior lobe is combined with an extirpation of areas 4 and 6 of the cerebral cortex, conspicuous and enduring spasticity ensues in the extremities opposite to the precentral lesion. Recent electrical studies by Snider and Stowell (Fed Proc, 1942, 1: 82), subsequently confirmed by Adrian (Brain, 1943, 66: 289), suggest functional localization in the anterior lobe arranged in anterior-posterior direction with sacral and lumbar segments anteriorly situated (in lingula and centralis) and upper extremities in the culmen. Primary ablations of culmen or centralis on the macaque have given equivocal results as far as localization is concerned (Connor, Proc Soc exp Biol Med, 1941, 47: 205), but when carried out following unilateral ablation of areas 4 and 6, the upper extremity opposite the cerebral lesion becomes predominantly spastic when the cerebellar lesion is limited to the culmen, and the lower extremities when the lesion is limited to centralis. H-T Chang (in press, J Anat) finds in the spider monkey that spinocerebellar projections from the tail pass primarily to the lingula. The results of anterior lobe ablation in the macaque thus harmonize with functional localization suggested by electrical studies [Aided by a grant from The Rockefeller Foundation to V Soriano and The Fluid Research Fund, Yale Univ School of Medicine].

The effective osmotic pressure of the plasma proteins in mammalian capillaries. A SORRIVERA (by invitation) and J R PAPPENHEIMER, Dept of Physiology, Harvard Medical School. The hindlegs of cats and dogs were perfused with heparinized blood from a pump-lung circulation. The legs were suspended on a recording balance and the rate of fluid movement determined from the rate of change of weight. The arterial and venous pressures could be adjusted to any desired constant values. For any given protein concentration there exist an infinite number of pairs of values of arterial and venous pressures at which the leg neither gains nor loses weight. From two or more pairs of such values it is possible to determine many quantities associated with the mammalian capillary circulation which have not previously been measurable. Among them is the capillary pressure at which neither filtration nor absorption occur and this we call the *isogravimetric capillary pressure*, its value may be determined with an error of less than 1.0 mm Hg. During the first three hours of perfusion the isogravimetric capillary pressure is  $95 \pm 2\%$  (SD  $\pm 6\%$ ) of the osmotic pressure of the plasma proteins. This is true over the range of osmotic pressures so far investigated (12.0 to 28.5 mm Hg). Knowing the isogravimetric capillary pressure it is possible to set the mean capillary pressure to known values by altering the arterial or venous pressures. The rate of filtration or absorption thus produced is found to be pro-

portional to the difference between the mean capillary pressure and the isogravimetric capillary pressure, it is independent of the absolute value of the protein osmotic pressure.

The ratio between total circulating hemoglobin and total plasma protein. C R SPEALMAN, M NEWTON (by invitation) and R L POST (by invitation) School of Medicine, Univ of Pennsylvania. The value for the ratio between quantity of hemoglobin and quantity of plasma protein in a sample of blood can be calculated from determinations of hemoglobin concentration, plasma protein concentration and hematocrit (eq 1)

$$(1) \quad R = \frac{Hb_{conc}}{Pr_{conc}(1 - \text{hematocrit})}$$

This value also represents the ratio between total circulating hemoglobin and total plasma protein, if the quantity of hemoglobin relative to protein is constant at all points throughout the circulatory system of the subject under study. Theoretical considerations make such a constancy unlikely. However, it may be that the ratio existing in a sample of blood taken from a given point in the circulatory system (vein) is proportional to or unimportantly different from the ratio existing in the total circulating volume of blood. If such is the case, the ratio (R) of equation (1) may be used as an index of changes in relationship between quantity of circulating hemoglobin and quantity of plasma protein.

Data obtained following plasma infusion, epinephrine infusion, hemorrhage, meals, changes in posture or in environmental temperature, etc, suggest that this ratio is altered greatly only by procedures which alter the quantity either of circulating hemoglobin (determined by CO) or of plasma protein. The tentative conclusion is that this ratio as determined by our procedures is a measure of the ratio between total circulating hemoglobin and total plasma protein and may be used as an index of changes in relative amounts of these substances. [Work carried out under a Life Insurance Medical Research Fund grant to Professor H C Bazett].

Changes of the electrical discharges of the hypothalamus and midbrain tegmentum in cerebral concussion. E A SPIEGEL, A J LEE (by invitation), M MARKS (by invitation) and M SPIEGEL-ADOLF (by invitation) Depts of Exp Neurology and Colloid Chemistry, Temple Univ Medical School, Philadelphia, Pa. A number of physiological changes induced by cerebral concussion such as disturbance of consciousness, changes of body temperature, hyperglycemia, suggest impairment of the hypothalamus, while loss of labyrinthine and body righting reflexes (Spiegel and Spiegel-Adolf, Fed Proc 5: 98, 1946) point to involvement of the tegmentum mesencephali. In

order to ascertain whether these regions are affected in cerebral concussion, their electric discharges were recorded by means of needles implanted by the aid of a stereotaxic apparatus in the base of the skull. For a study of the electrical activity of the cerebral cortex, phonograph needles were inserted in the skull. Acceleration concussion was produced by blows applied to the head of the freely swinging animals (cats). Following concussive blows, the changes of the electrical activity of the hypothalamus and midbrain tegmentum (reduction of the amplitude or abolition of all electrical activity, appearance of slow waves, of bursts of groups of high amplitude waves) were quite similar to the electrical disturbances recorded from the cerebral cortex. Injury of the mesencephalon and diencephalon is also indicated by histopathological studies in conjunction with Dr H T Wycis in which several days or weeks after cerebral trauma proliferation of the fibrous glia in the region around the Sylvian aqueduct or the third ventricle could be demonstrated [Aided by a grant from the John and Mary R Markle Foundation]

**Influence of medication upon blood pressure in seasickness** E A SPIEGEL and A SOKALCHUK (by invitation) *Temple Univ School of Medicine, Philadelphia, Pa*. Attempts to prevent or treat seasickness or other forms of motion sickness as a rule are directed only against the most prominent phenomenon of this syndrome, vomiting. Since seasickness usually is associated with a fall of blood pressure in the majority of cases (see the measurements by Sokalchuk in this volume), a combination of drugs effective in counteracting the gastrointestinal effects (scopolamine, bellafoline) with phenobarbital and a vasoconstrictor drug was used in an attempt to restore blood pressure to normal in seasickness. Paredrine hydrochloride was chosen as the vasoconstrictor. Previously it was shown in dogs and cats that this drug is able to prevent for several hours the depressor effects of labyrinthine stimulation upon the blood pressure (Oppenheimer and Spiegel, *Arch Internat Pharmacodyn* in print). In 41 experiments this combined medication was administered to 33 severely seasick individuals after development of symptoms. The depressed systolic blood pressure partially or completely returned to normal in 23 tests (56%), in 8 of these 23 tests the restoration of the normal pressure was followed by a slight rise 14 times (34%) a further fall of the pressure occurred during the continued illness. In 2 cases the rise during seasickness was increased on medication, in one instance of increased blood pressure the reaction was reversed, and in one case the medication failed initially to restore the depressed blood pressure, but brought it back partially in a later experiment.

**Adaptation to a substrate in the absence of its utilization** S SPIEGELMAN, JOHN M REINER (by invitation) and M SUSSMAN (by invitation) *Dept of Bacteriology, Washington Univ, School of Medicine, St Louis, Missouri*. A question of some importance to our understanding of the mechanism of enzymatic adaptation centers around the problem of whether a cell can form an enzyme for a substrate it cannot use.

An opportunity of investigating this problem was provided by the case of adaptation to maltose fermentation by *S. cerevisiae*. In agreement with previous results we found that our fully adapted cultures could not ferment maltose at high pH. Cultures which possessed  $Q_{CO_2}^N$  values of 200 or above on maltose at pH 4.5 possessed no measurable capacity to ferment this carbohydrate at pH values of 8.1 and above. Accordingly, experiments were performed in which maltozymase activity was measured subsequent to various periods of incubation at pH 8.5. All of these experiments were carried out under completely anaerobic conditions in Warburg manometers. To provide a source of energy for the adaptation small amounts of glucose (15 mg) were provided with the maltose, both being added simultaneously from the same side-arm. When all  $CO_2$  evolution (due to the added glucose) had ceased, sufficient acid to adjust the pH to 4.5 was added from the second side-arm. As determined by controls to which no maltose had been added, the evolution of the retained  $CO_2$  was complete within 15 minutes. Subsequent to this period any  $CO_2$  evolution could only be due to the fermentation of maltose. In all cases it was possible to demonstrate that the incubation period with the maltose at the high pH resulted in the appearance of measurable enzyme activity. The rates attained ranged between  $Q_{CO_2}^N$  values of 30 and 50.

These experiments would seem to indicate that it is possible for a cell to form an enzyme in response to a substrate which it cannot use.

**Experiments on the Eve rocking method of artificial resuscitation** ROBERT K SPIRO, ROBERT S AARON and JOHN S THOMPSON (introduced by J Raymond Johnson) *Laby of Physiology, Long Island College of Medicine*. In a study of certain aspects of the efficiency of the Eve rocking method of artificial resuscitation, experiments were carried out to determine (1) tidal air and minute volume ventilation at rest and during rocking, (2) alveolar  $O_2$  and  $CO_2$  levels before and after a period of rocking, (3) effects of altering the rate and rhythm of rocking, and (4) comparative results of rocking during normal and relatively apneic states.

Subjects were fastened securely in a supine position on a see saw rocker and connected to a spirometer for recording tidal air and pulmonary ventilation. Through proper valve controls, alveo-

lar air could be sampled at any moment. Rocking was performed at a rate of 12 cycles per minute and at an angle of  $30^\circ$  from the horizontal.

In 15 subjects tidal air increased 37 to 325% during rocking. Minute volume increased much less due to the slower than normal rate of respiration. Alveolar  $O_2$  and  $CO_2$  showed little variation from resting values in 8 experiments. Several variations in the rate and rhythm of rocking gave no better results than the regular 12 per minute cycle.

Rocking was carried out on 3 subjects in whom relative apnea had been produced. During this state rocking tidal air values were approximately the same as those during the normal state. Alveolar  $CO_2$  values showed a slower return to normal than when the subjects were allowed to recover without rocking, due to the greater pulmonary ventilation.

The comparative susceptibility of cats and dogs to anoxia. R. W. STACY and W. V. WHITEHORN (introduced by Fred A. Hitchcock). *Dept of Physiology, Ohio State Univ., Columbus*. A difference in the tolerance of cats and dogs to anoxia produced by rebreathing air ( $CO_2$  absorbed) has been demonstrated. When respiratory failure occurred the per cent oxygen in the inspired air was 2.6 for intact dogs, 4.7 for intact cats, 7.0 for dogs after denervation of the carotid sinus area and section of the vagi, and 7.8 in similarly treated cats, while the per cent saturation of the arterial blood was, in intact animals, 11.6 for dogs and 7.5 for cats, and in denervated animals, 10.1 for dogs and 8.5 for cats. In intact animals ventilation volume increased 373 per cent for dogs and 54 per cent for cats, while in denervated animals the increases were 34 per cent for dogs and 21 per cent for cats. From the per cent saturation of the arterial blood we may estimate that, in both species, respiration fails when the  $pO_2$  of alveolar air is about 10 mm of Hg. By the marked increase in ventilation volume the dog is able to maintain this alveolar  $pO_2$  with a  $pO_2$  of only 18 mm in the respired air, while the cat requires 32 mm  $pO_2$  in the inspired air to maintain the same alveolar  $O_2$ . These results indicate that the basis for the species difference between dogs and cats is the greater response of the dogs' respiratory mechanism to chemoreceptor stimulation.

The *in vitro* inhibition of cytochrome oxidase by azide and cyanide. J. N. STANNARD and B. L. HORECKER (by invitation). *National Inst of Health, Bethesda, Maryland*. The inhibition of rat heart cytochrome oxidase by azide and cyanide was studied as a function of pH, using a spectrophotometric method involving the oxidation of ferrocytochrome c. In the case of cyanide the degree of inhibition is independent of pH within physiological limits, while the inhibition by azide is sensitive to pH. It was established, from application of the

mass law to the hydrolysis of salts of cyanide and azide, that in both cases the inhibition is related to the concentration of the undissociated acid, HCN or  $HN_3$ . In this respect cytochrome oxidase differs markedly from cytochrome c or methemoglobin where combination is with the ion (see abstract on the cytochrome c-azide complex).

The inhibition reaches 50 per cent at about  $5 \times 10^{-7}$  M of either HCN or  $HN_3$ , which is equivalent at pH 7.4, to approximately  $5 \times 10^{-7}$  KCN or  $2 \times 10^{-4}$  NaN<sub>3</sub>. In both cases the effect follows closely the mass law expression assuming combination of one acid molecule with one of enzyme.

Azide, but not cyanide, was observed to catalyze the oxidation of ferrocytochrome c in the absence of enzyme. The catalytic effect is due to the presence of traces of inorganic Fe, the Fe azide complex forming a reversible oxidation-reduction system which is rapidly reduced by ferrocytochrome c and slowly oxidized by atmospheric oxygen.

Tetraethyl ammonium—potassium antagonism in the mammalian heart. H. STANSFIELD (by invitation) and H. E. HOFF. *Dept of Physiology, McGill Univ., Montreal*. Loewi (J. Pharm. Exper. Therap. 88: 136-141, 1946) has reported that the depressant action of KCl on the frog's heart is antagonized by tetraethyl ammonium bromide (TEA). Acheson and Pereira (J. Pharm. Exper. Therap. 87: 273-280, 1946) state however that while TEA can block the ganglionic stimulating action of acetylcholine in the superior cervical ganglion of the cat, it cannot block the ganglionic stimulating action of potassium ions.

Two series of experiments were performed to study the antagonism, if any, of TEA to potassium poisoning in mammals.

The toxic effects of potassium on the mammalian heart have been described by Winkler, Hoff and Smith (Amer. J. Physiol. 124: 478-483, 1938). The stages of potassium poisoning can be followed electrocardiographically.

In 6 dogs the ureters were ligated to prevent excretion, and isotonic KCl was run in slowly, intravenously, until the stage of intoxication marked by loss of P waves was reached. Injections of TEA at this point brought transient return of a normal ECG pattern. The P waves normally disappear at a potassium level of 9-11 m eq/l. With TEA the P waves have been brought back transiently at concentrations as high as 12.5 m eq/l. Typical death by potassium arrest at the expected range of potassium concentrations was avoided only on animals killed by too rapid or too large an injection of TEA.

Dogs made anuric by aspecific ligation of both ureters developed the electrocardiographic evidence of early potassium poisoning in 2-3 days, with loss of P waves at a potassium concentration of approximately 9.5 m eq/l. Dosage of TEA suffi-

cient to return the E C G to a normal pattern caused convulsions, respiratory arrest and death.

An extension of the "Law of Denervation" to afferent neurones GEORGE W STAVRAKY and CHARLES G DRAKE (by invitation) *Dept of Physiology, Univ of Western Ontario Medical School, London, Canada* According to the "Law of Denervation" which was suggested by Cl Bernard and formulated by Cannon "When, in a series of efferent neurones a unit is destroyed, an increased irritability to chemical agents develops in the isolated structures." In order to ascertain whether this increase of irritability occurs only after section of efferent connections, or whether deafferentation too, leads to a greater irritability of corresponding spinal neurones, in 12 cats the left hind limb was deafferented by aseptic intradural section of L to S dorsal roots, and after various periods of time the brain was pithed and the contractions of both quadriceps muscles recorded. Beginning 18 hours after deafferentation (longest time 3 months), intraortic injections of acetylcholine, adrenaline, strychnine, metrazol and camphor evoked greater responses on the deafferented side—the contractions appeared after smaller quantities of the drugs, started earlier, were more powerful and lasted longer than those on the intact side. Acute unilateral deafferentation, carried out immediately preceding the recording, reduced the effectiveness of the chemical agents on the corresponding side.

In another series of experiments on 6 chronic cats in which deafferentation of the forelimb was carried out by section of C<sub>3</sub> to T<sub>1</sub> dorsal roots, intravenous injections of the same drugs lead to asymmetrical contractions of the forelimbs—the deafferented limb responding first, swinging higher towards the head, and becoming more rigid during the contraction, the effects resembling somewhat those described in the case of frontolobectomized and semidecerebrated animals (Stavraky, G W, *Trans Roy Soc Canada* 37 127, 1943, *Federat Proc* 5 100, 1946).

The pH of synovial fluid in the anaesthetized dog under treatment with metrazol and insulin I E STECK (by invitation), N R JOSEPH (by invitation), and C I REED *Dept of Physiology and of Medicine, Univ of Illinois, Chicago Colleges* Determinations of pH in the knee joint and femoral venous blood of anaesthetized dogs were carried out before and after the administration of metrazol or insulin in doses sufficient to produce convulsions. In the resting state before the injection of either drug, neither blood and synovial fluid pH fluctuated by more than about 0.05 over a period of 15 or 20 minutes. Metrazol injections generally resulted in severe convulsions within a few minutes. Immediately after the onset of convulsions, the joint pH fell rapidly, the maximal change

varying from about 0.3 to 0.6. Blood pH was lowered by only a fraction (approximately one fourth) of the corresponding change of joint pH. Over a period of time, there was little parallelism between the curves of blood pH and joint pH, the fluctuations of the latter being more pronounced and having a sharper downward tendency. Insulin injections were generally effective only after a period of 1½ or 2 hours. During the convulsive period, effects resembling those observed in metrazol convulsions were noted, the changes of joint pH being far more pronounced than those of blood pH. The results in both cases can be interpreted as indicating a flow of acid metabolites from active muscles into the joint cavity at a rate greater than that of its removal by the circulation.

The effects of the introduction of gas into the colon on its pressure and activity F R STEGERDA and W C CLARK (by invitation) *Dept of Physiology, Univ of Illinois, Urbana, Illinois* By means of an open tipped tube placed in the lower colon and connected with a recording manometer, the effects of distention with various amounts of gas on the total pressure and onset of tonic activity can be recorded.

Although there are variations between individuals, it would seem that when 200 cc of air are injected into the lower colon a pressure of 20 to 25 cm of water is created which remains relatively unchanged with succeeding administrations of similar amounts of gas up to a total of 1,000 or 1,200 cc. When a volume of approximately 600 cc of gas has been reached, rhythmical contractions of the colon occur and increase in amplitude with increased amounts of gas. The increased distention of the colon under these conditions is not accompanied by any distress because of the compensating outward distention of the abdominal wall.

Apparatus to make similar pressure recordings in the stomach and small intestine is being constructed.

Some effects of cytochrome C on the oxygen economy of anesthetized dogs A J STEIGMAN (by invitation), A SOKALCHUK (by invitation), D ELLIS (by invitation), and E M GREISHEIMER *Temple Univ School of Medicine* Alterations in the oxygen economy of anesthetized, heparinized dogs were studied following the intravenous administration of crude cytochrome C, from horse heart. The anesthetic used was pentobarbital sodium and urethane. An endotracheal catheter with cuff and spirometer permitted the measure of oxygen consumed.

Femoral arterial samples were collected by cannula, and mixed venous samples were obtained (by catheter) from the right ventricle. Oxygen was determined by the van Slyke Neill method. In addition to oxygen consumption, the coefficient of



the probable nature of the estrogen present are taken into account

These results, together with the grossly elevated levels seen in pregnancy urine, indicate that a low kidney threshold exists for the estrogenic steroids. Furthermore, it seems possible that in the postulated estrogen-estroprotein equilibrium in human blood and in the blood of other species, the protein-bound material may serve as an active reservoir of estrogen which is potentially available for physiological action, but protected from immediate excretion by the kidney. [Aided by a grant from the Penrose Fund of the American Philosophical Society]

**The intestinal pH threshold for regulation of gastric emptying** J E THOMAS *Dept of Physiology, Jefferson Medical College* Previous communications from this laboratory have shown that acid in the intestine inhibits gastric secretion when the intestinal pH is between 2.0 and 2.5. Two types of experiments were performed to determine the pH threshold for inhibition of gastric emptying in dogs. (1) Three hundred cc of acid solution buffered with gastric mucus or egg white (pH 1.5-1.8) were placed in the stomach and recovered from the intestine, and the volume and pH of the intestinal drainage measured. From 75 to 150 cc were emptied from the stomach during the first 10 minutes with the intestinal pH between 2.0 and 3.0. Only one sample in 12 experiments was obtained with a pH below 2.0 and only 2 above pH 3.0. (2) Graphic records of gastric motility before and after feeding were obtained while perfusing the duodenum with buffered solutions of acid and the pH of the perfusate measured after it was recovered from the intestine. Gastric motility was progressively inhibited as the intestinal pH fell from 3.0 to 2.0 and completely abolished at pH 2.0. There was no effect above pH 3.0. It is concluded that, in the absence of other stimuli, an intestinal pH of 3.0 is required to modify gastric emptying and that emptying ceases at pH 2.0, also that gastric motility, gastric secretion, and gastric emptying are influenced in a parallel manner by acid in the intestine.

**Carbohydrates as stimuli for the secretion of pancreatic enzymes** J E THOMAS and J O CRIDER *Dept of Physiology, Jefferson Medical College* Carbohydrates in the intestine are not, by themselves, adequate stimuli for the pancreas but they may modify the effects of other stimuli. Babkin and Savich (*J Russ d Physiol* 3: 143, 1921) found that sugar increased the enzyme content of the juice secreted in response to HCl. A similar action of starch with secretin in anesthetized cats was reported by Harper and Vass (*J Physiol* 99: 415, 1940). The combined effect of various carbohydrates and secretin was studied in 4 chronic fistula dogs. Secretin was given by con-

tinuous intravenous injection and after a control period the carbohydrates were injected into the intestine. Results were calculated in terms of total nitrogen output from the pancreas. All preparations used increased the nitrogen output by increasing either the volume or the concentration, or both, of the pancreatic juice. The average percentile increase over the average output of nitrogen during the control period with the various preparations was: soluble starch, 34; starch plus pancreatic juice, 123; dextrin (N F V, Baker) 87; dextrin (Bacteriological, Pfanstiehl) 71; dextrin (Reagent, Merck) 37; maltose, 93; lactose, 60. Control experiments with saline remain to be done but the available data prove that at least some carbohydrates increase the output of enzymes, as indicated by total nitrogen output, in the presence of secretin. Moderate doses (0.2 mg/kg) of atropine or hyosecyamine given during the action of the carbohydrates reduced the nitrogen output to the control level or below.

**The effect of diet on respiration and respiratory enzymes of liver from hyperthyroid rats** SAMUEL R TIPTON *Dept of Physiology & Pharmacology, Medical College of Alabama, Birmingham 5, Alabama* In continuation of our study of succinate and cytochrome oxidation systems under varied endocrine conditions, we have subjected hyperthyroid rats and adrenalectomized rats to diets varying with respect to components of the B group of vitamins. Hooded rats made deficient in the total B-complex, and also those on a diet deficient only in riboflavin showed a significant decrease in activity of the succinic dehydrogenase of liver with little change in cytochrome oxidase. In hyperthyroid rats maintained on these two diets both enzyme systems showed 10-15 per cent lower activity than those found in hyperthyroid rats on a normal diet. Control rats were restricted to approximately the same caloric intake as the rats on experimental diets.

Thiamin deficient rats showed no significant difference in enzyme activity from control rats, but the mobilization of liver succinic dehydrogenase in hyperthyroid rats was depressed significantly. Thiamin deficiency resulted in a greater weight loss and higher mortality in hyperthyroid rats. Thiamin in excess of the normal requirements given to hyperthyroid rats prevented weight loss and gave lower mortality but did not increase significantly the hyperthyroid enzymatic activity.

All three groups of rats showed a small but significant depression in QO of liver slices with pyruvate and succinate as substrates when compared with liver slices from rats on a normal diet.

Our results suggest that some or all components of the vitamin B complex are necessary for the mobilization of succinic dehydrogenase and cytochrome oxidase which occurs in hyperthyroidism.



[This work was aided by a grant from Ciba Pharmaceutical Products, Inc.]

**Effect of BAL in preventing alloxan-diabetes in rats** R TISLOW and ANNETTE CHESLER (by invitation) *Biological Research Labs., Schering Corporation, Bloomfield, N J* BAL (British antilewisite), 2,3 dithiolpropanol prevented alloxan-diabetes in rats. Fifty-one mg/kg BAL injected intravenously into 60 gram Sprague Dawley rats 1 to 2 minutes before the intravenous injection of 60 mg/kg of alloxan monohydrate prevented completely the hyperglycemia and the decrease in growth rate observed in animals injected with alloxan alone. BAL was protective until the dosage was reduced below 20 mg/kg.

**Studies on the sodium, potassium and water content of tissues in the cockroach (*Periplaneta americana*)** JULIAN M TOBIAS *Univ of Chicago Toxicity Lab., and the Dept of Physiology* From the classical point of view that cellular membrane potentials depend largely upon a concentration difference between the potassium inside and outside of the cell, it seemed of interest to clarify the implications of the statement so often seen in discussions of insect haemolymph, that "Of the cations, sodium seems always to be replaced largely by potassium" (Wigglesworth—Principles of Insect Physiology). Therefore, the water, sodium and potassium content of whole haemolymph and serum (collected at the level of the prothoracic leg, ventral to the ventral diaphragm so as to get fluid bathing the nerve cord), nerve cord and leg muscle (cova) have been measured in the cockroach (*Periplaneta americana*).

In millimoles per liter of tissue water, the values obtained for haemolymph, serum, nerve cord and muscle were sodium 169, 107, 83.9, and 45.6, potassium 27.1, 17.3, 14.0 and 11.2. Thus, both muscle and nerve cord are seen to contain much more potassium and less sodium than the circulating fluid. There are, therefore, no indications from these data that the cation concentration gradient which may exist between irritable tissue and its environment is fundamentally different (except quantitatively) in the insect from what it is in other forms.

**Observations on the use of the oxygen cathode** JULIAN M TOBIAS and ROSEMARY HOLMES (by invitation) *Univ of Chicago Dept of Physiology and Toxicity Lab.* Preliminary experiments with the exposed type of flush, platinum wire, oxygen cathode, described by Davies and Brink, have largely confirmed their findings (R S I 13 524, 1942). An electrode, 40 micra or larger in diameter, requiring no amplifier if used with a sensitive galvanometer, can, in Ringer's solution, measure, with great precision, a change in oxygen tension of some 3.3 mm of Hg. This corresponds to a change of about 0.1 cmm of oxygen per cc, approximately

the same sensitivity obtained with other standard types of microrespirometers. Such an electrode responds to changes in environmental oxygen in less than one second. When used in a protein solution such as plasma, there is a progressive "desensitization" of the electrode which can be largely eliminated if it be covered with a thin film of collodion.

The electrode, mounted in a hypodermic needle, has been used to follow changes in subcutaneous and intramuscular oxygen tensions in animals breathing various oxygen mixtures. The data are, however, difficult to interpret since current change in response to a given change in the respiratory mixture frequently undergoes a progressive decrease both in rate and magnitude. The highest degree of reproducibility in the intact animal has been achieved with the electrode in contact with the mucosa of the eyelid, lip or vagina. Thus, with an electrode applied to the eyelid mucosa, as the respiratory mixture was changed a number of times between air and 100% oxygen, over the period of an hour or so, the accompanying current changes were reproducible with a standard error of 3%.

**Thromboplastin in the urine of normal and hemophilic men** LEANDRO M TOCANTINS and JOHN N LINDQUIST (by invitation) *Jefferson Medical College, Philadelphia* The clear, protein and cell-free (Berkefeld filtration) fresh human urine, spontaneously voided, or collected from the renal pelvis by ureteral catheterization, contains a substance (or substances) which shortens the rate of blood coagulation by accelerating the conversion of prothrombin to thrombin. Urine from hemophiles has as high and sometimes higher clot accelerating activity as urine from normal men. The clotting times of hemophilic and normal blood or plasma in collodion tubes are rendered equal by the addition of undiluted, intact or dialysed urine (one part of urine to ten of blood). The thromboplastin activity is preserved in urine rid of most of its solutes by dialysis (48 hours against H<sub>2</sub>O). The activity is enhanced by concentration of the urine, diminished by heat (55°C—15 minutes) and almost destroyed at 70° (15 minutes). Unlike dilute solutions of aqueous brain extracts which lose their thromboplastic activity rapidly on standing, the intact or dialysed urine thromboplastin maintains its activity for several days if kept in the cold, with a preservative. The thromboplastin of the urine may be derived from the kidney itself, or represent the product of disintegrated tissue or blood cells cleared from the circulating blood by excretion in the urine.

**The body temperature-arterial pressure relationship in the chicken** M TOLPIN (by invitation) and S ROXBARD *From the Cardiovascular Dept., Research Inst., Michael Reese Hospital and the Dept of Physiology, Univ of Chicago, Chicago,*

*Illinois* Previous work from this laboratory has shown a direct relationship between body temperature and arterial pressure of the turtle, and that this relationship depended upon the mediation of centers in the brain. This work has been extended to other animals, and results on the chicken, *Gallus domesticus*, are given below.

Cooling of the birds by means of ice packs caused a fall in pressure and heart rate, rewarming by radiant heat caused a return to the original levels. Heating above normal body temperature caused a rise in blood pressure and heart rate until a critical level of about 44°C was obtained. With further increase in temperature the blood pressure fell sharply, although the heart rate continued to increase. Administration of epinephrine at this time caused a transient rise in pressure, and the bird appeared to revive momentarily.

Temperature (°C)	Arterial pressure (mm Hg)	Heart rate (beats/min)
25	102/92	110
35	115/108	330
41.5	130/115	460
43	145/125	540

These results show that the body temperature-blood pressure relationship hold for a bird, the chicken. This relationship is independent of the heart rate. The fact that a rise in pressure can be elicited terminally by epinephrine suggests that the fall in pressure at high temperature levels depends upon the failure of vasomotor centers rather than the peripheral blood vessels.

**Nerve conduction block by di-isopropyl fluorophosphate (DFP) and eserine without change in demarcation potential.** JAMES E. P. TOMAN, J. WALTER WOODBURY (by invitation), and LOWELL A. WOODBURY (by invitation). *Dept of Physiology, Univ of Utah School of Medicine, Salt Lake City, Utah*.<sup>1</sup> Bullock *et al* (*J Neurophysiol* 9, 9, 253, 1946) and Crescitelli *et al* (*J Neurophysiol* 9, 241, 1946) reported that high concentrations of the anticholinesterases eserine and DFP block conduction in nerve. Bullock *et al* concluded that anticholinesterases which penetrate nerve may block conduction by preventing the hydrolysis of acetylcholine, thereby causing an enduring depolarization, but no measurement was made of the assumed depolarization. In the present studies, demarcation potential was not significantly changed when segments of frog sciatic nerve were treated with concentrations of eserine sulfate or DFP just sufficient to block completely the conducted action potential. The onset of DFP block was associated

with an increase in threshold, a slight decrease in conduction velocity and relatively little change in the recovery process. Spontaneous firing never was observed at any stage of DFP block. The results do not support the conception of acetylcholine as a primary depolarizing agent essential to impulse propagation in nerve.

**Effect of amino acids on muscle function of patients with myasthenia gravis.** CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts of Medicine (Neurology) and Psychiatry, Cornell Univ Medical College, New York, N. Y.* According to a recently presented concept much of the symptomatology of patients with myasthenia gravis can be explained by a decreased acetylcholine synthesis in these patients. Amino acids were found to increase acetylcholine synthesis *in vitro*. It seemed reasonable, therefore, to investigate the effect of infusion of amino acids on patients with myasthenia gravis.

Muscle action potentials were recorded of healthy subjects and six patients with myasthenia gravis following stimulation of the ulnar nerve by ten stimuli per second, each of 100 microsecond duration and of "supramaximal" intensity.

The amplitude of muscle action potential in healthy subjects was maintained during electrical stimulation of the ulnar nerve. In two severely sick patients with myasthenia gravis the drop of the amplitude of the action potential was large and predictable. This could be used for testing the action of various agents of the muscle function of these patients. When action potential records were taken after infusion of amino acids (one liter of 5 per cent Amigen (Mead & Johnson) solution containing 5 per cent dextrose), the records of these patients with myasthenia gravis resembled the muscle action potential records of healthy persons.

The above results suggest that amino acids may improve muscle function in patients with myasthenia gravis. The mechanism of this action, whether improved acetylcholine synthesis, correction of an amino acid deficiency, detoxifying effect of amino acids, is under investigation.

**Pressor substances in dog plasma incubated with renin.** ELEANORE TRIPP (by invitation) and ERIC OGDEN. *Dept of Physiology, Univ of Texas School of Medicine, Galveston*. One or two c.c. of dog plasma were mixed in a syringe with an appropriate quantity of hypertensinase-free hog renin. Half of this quantity was immediately injected intravenously into a pithed cat to control any rise of blood pressure produced by the renin. This was negligible in the doses used. Ten minutes later the remainder of the mixture was injected and the rise of blood pressure (15 to 30 mm Hg) used to estimate the substrate content of the plasma. These rises were compared with the response to a standard preparation of angiotonin from which the

<sup>1</sup> Assisted by grants in aid of research from the U. S. Public Health Service and the University of Utah School of Medicine Research Fund.

protein had been removed by alcohol precipitation. The plasma samples from the normal dog (if free from visible hemolysis) showed little variation from month to month and from individual to individual. Furthermore frozen plasma retained its substrate content. Adrenal insufficiency consistently lowered the substrate content as previously reported (Collings, Ogden, and Taylor).

When the testing was done on cats of low sensitivity it was found that a large dose of a fresh plasma-remun mixture would elevate the blood pressure to a higher level than could be obtained from the injection of any amount of the angiotonin preparation. This suggests that the latter preparation was completely lacking some pressor material resulting from the renin and substrate reaction. [Acknowledgment is made to the John and Mary R Markle Foundation.]

Further analysis of the gasp reflex. ROBERT D TSCHIRGI (introduced by R W Gerard) *Dept of Physiology, The Univ of Chicago*. Gaspings of the severed rat head has been used by several workers as an index of activity of medullary respiratory centers. Present experiments establish the reflex character of gasping in several types of anoxia and locate the actions of anoxia and hypercapnia in the reflex arc.

After decapitation, cyanide administration, or inhalation of oxygen-free gas mixtures, gasping occurs when the carotid bodies remain functionally connected with the medulla but is entirely absent when they are disconnected. Gaspings is terminated by central failure, for the carotid receptors discharge long after gasping ends, and the lingual-mandibular reflex (engaging the same efferent arc) also outlasts it.

Discharge time (from first to last gasps) decreases with age. For 11-day rats inhaling pure nitrogen, it averages 142 sec, as compared with 200 after decapitation. Addition of  $\text{CO}_2$  to the  $\text{N}_2$  (but not to  $\text{O}_2$ ) increases discharge time, to a maximum 320 sec at 35 per cent  $\text{CO}_2$ . That the prolongation depends on anaerobic processes is shown by the ability of iodoacetate to cut discharge time to 25 sec, whatever the  $\text{CO}_2$  concentration.

By "perfusing" the carotid bodies of one rat with the blood of a second and varying independently the gas inhaled by each, the medullary centers and the carotid bodies of an animal were exposed to different conditions. Anoxia both of the brain and the carotid body must be present for gasping to occur. The potentiating action of  $\text{CO}_2$  is exclusively on the carotid body.

These findings, while establishing important peripheral factors in the gasp response, do not vitiate its use in investigation the action of central neurones.

The effect of ergotamine tartrate on potassium tolerance. CAROLINE TUM SUDEX *Boston Univ*

*School of Medicine, Dept of Physiology*. For intact rats an average of 27 intravenous injections of 0.05 ml of 2% KCl/100 grams body weight, given at 5 minute intervals, were required to produce a fall of over 60% in mean arterial pressure. In rats treated with ergotamine tartrate (0.5 mg/100 grams) and in rats bearing grafts of adrenocortical tissue only, 3 to 8 (aver  $\pm 5$ ) injections produced threatened circulatory collapse. After 10 mg histamine/100 grams body weight an average of 9 injections caused severe depression.

At the time of collapse the plasma potassium attained equally high levels in normal, histamine-treated rats and rats with only adrenocortical tissue, namely,  $29.8 \pm 3.0$ ,  $28.5 \pm 2.2$  and  $28.1 \pm 2.2$  mg % respectively. The level, however, was definitely lower in rats subjected to ergotamine, namely,  $23.8 \pm 1.7$  mg %. The increased susceptibility of the ergotamine-treated rats to potassium was further enhanced by histamine (10 mg/100 grams) such that a single injection of KCl produced prompt circulatory failure.

No change in potassium sensitivity was found in 3 of 6 similar experiments using dehydroergotamine tartrate (DHE-45). The more transient action of DHE-45 and an initial depressant tendency on blood pressure in contrast to ergotamine seem accountable for some of the variability and differences observed. Further experiments may indicate whether or not enhanced sensitivity to potassium is typical of sympatholytic agents in general, especially in circumstances demanding adequate adrenocortical activity.

QT changes following exercise. WILLIAM G TURMAN (by invitation), IRVING L ERSHLER (by invitation), and JANE S ROBB *Depts of Pharmacology and Medicine, College of Medicine, Syracuse Univ, Syracuse, N Y*. In 1941, Blair, Wedd, and Young suggested that the QT interval may be a more sensitive index of cardiac muscle state than is heart rate. Schlamowitz later reported a linear relationship between QT interval and cycle length, both at resting rates and following exercise.

Many QT values for 500 athletes collected at this University by Ershler and Turman, fall below the normal curve of Ashman and Hull. These and unpublished data of Young for 30 healthy young women at Mt Holyoke (courtesy of Dr Mary Maxfield) are equally dispersed about the line of Schlamowitz.

The next step in testing Blair's hypothesis was to obtain QT values after exercise in older individuals and in those known to be either in potential or borderline decompensation.

The Brouha score for Young's group ranges from 45 to 97, while in those less physically fit it ranges from 35 to 54. The latter group show two main types of response to exercise, (a) the main change is in rate with no or very slight QT lengthening

following an initial shortening, and a slow return of both QT and rate to resting values, and (b) the main change is a less rapid rate, exceedingly brief shortening of QT with far greater subsequent lengthening, and very fast return of the QT interval to normal. The rate did not reach the resting level within the period of observation.

We believe QT may be a better index than rate alone when cardiac reserve is low, but further study will be necessary to establish the prognostic value. [This work was supported by a grant from the Life Insurance Medical Research Fund and the Hendricks Fund.]

**The "fatigue" of prolonged wakefulness**  
DAVID B TYLER *California Inst of Technology, Pasadena*. The results of 20 experiments involving 600 subjects show that, with the exception of the effect on the electrical activity of the brain, no significant physiological or biochemical changes are produced by experimental insomnia up to 112 hours. Blood sugar, hemoglobin, red and white cell count, body weight, and body temperature show little variation from the normal. The excretion of 17-ketosteroids, total nitrogen and creatinine, and the level of adrenal-like substances in the blood are little affected. No significant changes are found to occur in auditory acuity, static ataxia, flicker fusion frequency, or reflexes. The slight respiration, heart rate and blood pressure changes that occur can be attributed to the state of relaxation of the sleepy subject. The only effects on psychomotor performance found are those that indicate a reduced ability to maintain sustained effort and performance.

The most marked changes that occur during experimental insomnia are the psychological disturbances. These alterations in behavior are first noticeable between 30 to 60 hours of sleeplessness and are characterized by increased irritability, loss of memory, hallucinations or illusions, inattention. In the majority of the subjects these disturbances are mild. In some instances, symptoms resembling acute schizophrenia are produced during sleeplessness. [Work done under contract sponsored by the C M R between O S R D and Calif Inst of Tech.]

**The effect of benzedrine and certain barbiturates during prolonged wakefulness**  
DAVID B TYLER *California Inst of Technology, Pasadena*. Although a sleepless individual is capable of normal performance, as measured by a large variety of psychomotor tests, even after 100 hours of wakefulness, the indications are that he is not capable of maintaining a sustained performance. This effect, the decreased ability for sustained effort, first becomes noticeable after 48 hours of wakefulness. Examination of the results reveal that it is not due to deterioration in a particular skill but to the increased difficulty in staying awake during a prolonged psychomotor test.

If in a 112 hour experiment 10 mg of benzedrine are administered twice daily beginning the first day of the sleepless period, it is without any significant effect on either the performance of the men or on their ability to stay awake during the five day vigil. If benzedrine is administered commencing the 3rd day, an immediate improvement occurs in the ability of the subjects to stay awake and the deterioration in performance occurring at that time is checked. However, the same dosage maintained during the 4th and 5th days becomes less effective. The results indicate that the effect of benzedrine, at least under these conditions, is not on the skill per se, but through its anti sleep action.

One gr amytal or 2.5 gr V-12 (ethyl beta-methylallyl thiobarbituric acid) given every 12 hours during the first 48 hours of a 5 day sleepless period produces only slight alterations in performance. The indications are that these components of motion sickness preventives can be safely given to men under such conditions of stress. [Work done under contract sponsored by the C M R between O S R D and Calif Inst of Tech.]

**The effect of mental "activity" and experimental insomnia on the electrical activity of the brain**  
DAVID B TYLER, J GOODMAN (by invitation) and T ROTHMAN (by invitation) *California Inst of Technology, Pasadena*. Changes in the EEG were studied in 12 subjects at intervals during 112 hours of continuous wakefulness. The records were analyzed on the basis of per cent time frequency distribution (Brazier and Finesinger, J Clin Invest 23 303, 1944). This method was found to be an objective and easily verifiable procedure for studying the effects produced.

The changes in the state of "attention" as produced by mental multiplication problems increase the rate of the potential changes of the brain. During the control days, the increase in rate produced by such stimuli parallels the intensity of the mental "effort" and is regular and progressive.

Experimental insomnia also increases the rate of the electrical activity of the brain. This is first noticeable after 50 hours of wakefulness, and the rate increases progressively up to 75 hours. If a multiplication problem is given at 50, 75 or 100 hours of sleeplessness, the effect on the EEG is irregular and indicates that the capacity of the fatigued brain to further increase its rate of potential changes in response to the stimulus of a problem is reduced.

The effects produced by mental activity and by prolonged wakefulness are in the same direction, indicating that mental "effort" required for working a problem or for staying awake during experimental insomnia produces an increase in the rate of the potential changes in the brain. [Work done under contract sponsored by the C M R between O S R D and Calif Inst of Techn.]

**Effect of stimulation of carotid sinus region on**

absorption from small intestine EDWARD J VAN LIERE, J CLIFFORD STICKNEY and DAVID W NORTHUP *Dept of Physiology, School of Medicine, West Virginia Univ, Morgantown, West Virginia* The absorption of isotonic NaCl solution placed for 30 minutes in a Moreau loop of the lower intestine of 13 barbiturized dogs was studied The average blood pressure of these dogs was 123 mm Hg Absorption was then studied in 15 dogs while the carotid sinus region was continuously stimulated electrically, the average blood pressure of this group was 124 mm Hg The dogs in the control group were selected from a larger series to match with the average blood pressure found in the experimental group

The percentage fluid absorbed by the control dogs was 57.9 and chloride 64.8, in the experimental group the percentage absorption was 42 of fluid and 52.7 of chloride There was a statistically significant reduction of fluid and chloride absorption in the latter group

It has been shown by Bernthal and Schwind (*Am J Physiol* 143:361, 1945) that there is a reflex vasoconstriction in the intestine in response to excitation of carotid chemoreceptors This vasoconstriction probably caused a lessened amount of absorption in the experimental group

Uptake of plutonium, yttrium and strontium by the callus of healing bone fractures L VAN MIDDELSWORTH, D H COFF and J G HAMILTON (introduced by J M D Olmsted) *Divisions of Physiology and Medicine of the Medical School, and the Radiation Lab of the Univ of California, Berkeley* Plutonium, radioactive yttrium and radioactive strontium are all metals of considerable practical importance which localize in the skeleton Since the callus of a healing fracture passes through successive stages in bone formation, it was felt that the uptake of these elements by the callus might afford valuable information on their deposition in bone The left fibulae of adult male rats were fractured opposite the tibial spine Since this bone does not bear weight and is naturally splinted by the tibia, no postoperative care was necessary The animals were sacrificed after various time intervals from 2 to 15 days  $\text{Pu}^{239}$  and  $\text{Y}^{88}$  were injected intramuscularly at the time of fracture, or intravenously 2 days before the rats were sacrificed  $\text{Sr}^{89}$  was injected intraperitoneally 24 hours before the animals were killed The alpha emitting  $\text{Pu}^{239}$ , beta emitting  $\text{Sr}^{89}$  and gamma ray emitting  $\text{Y}^{88}$  could all be distinguished in the same bone sample by these differences in radiation

The uptake of each of these radioactive elements in the fractured fibula was compared with that in the unbroken control bone of the opposite side The ratio of these two values gave a measure of the concentration of each element in the healing callus Active uptake of plutonium and yttrium in the callus was observed on the second day, before

calcification or strontium localization had commenced Deposition of radioactive strontium in the callus began about the 4th to 5th day and reached a peak around 8 to 12 days when calcification was most active These differences suggest that the deposition of strontium is related to the activity of calcification, while some other mechanism is responsible for the deposition of yttrium and plutonium {This work was carried out under the auspices of the Manhattan Project}

Maturity induced by testosterone in the young male monkey G VAN WAGENEN *Dept of Obstetrics & Gynecology, Yale Univ School of Medicine, Yale University* The bone age of seven year old male rhesus monkeys is comparable to that of the human of twenty years During the sixth year the upper epiphyses of the long bones unite, the gonads contain mature sex cells and the pelage is that of the mature male Two experimental monkeys, two years and ten months old, presented the above signs of maturity From the beginning of treatment, seven months of age, weight and body length were accelerated At two years their weight was fifty per cent greater than the heaviest male records X ray films showed a massive increase in the musculature with an accompanying accentuation of contour and thickness of bone Body length, although it immediately rose from the average curve, did not exceed greatest normal length because of the imposed process of maturation which was thought to be a function of the androgen dosage

A testis of the control animal removed at two years eight months showed tubules containing only basal cells, while glands of the treated animals, two and three times as large, showed complete spermatogenesis The control mammary gland, one centimeter in diameter, was composed of spidery, thin-walled simple ducts The mammary gland of the treated animal was also of neonatal size, but the ducts stained heavily, were distended, and the terminal ends showed proliferating epithelium The silky, short hair characteristic of the young monkey changed to adult type during the second year and thereafter appeared longer and more luxuriant than that of the usual laboratory adult male

Effect of enterogastrone on gastric secretion of pyloric-ligated rats FRANK E VISSCHER and DONALD R RAYMAN (introduced by D J Ingle) *Research Labs, The Upjohn Company, Kalamazoo, Michigan* The ability of preparations of enterogastrone to inhibit gastric secretion may be observed in pyloric ligated rats (Friedman, M H F, and Sandweiss, D J, *Am J Dig Dis* 13:108 (1946)) Our method differs from that of Friedman and Sandweiss in several respects animals are fasted two days instead of one day, Cyclopal, 85 mg per kg, is used for anesthesia, injections are made at the time of pyloric ligation, gastric juice is collected at the end of two hours by removal and

drainage of the stomach, groups of five or six pairs of rats are employed for each experiment, solids are removed from the gastric contents by centrifugation, and the statistical significance of the observed inhibition is calculated

Our data concern the following effect of length of fast on volume of ingested solids, effect of solids on acidity of gastric juice, specificity of test for enterogastrone as determined by trial injections of a variety of substances and preparations, establishment of a dosage response curve for a sample of enterogastrone, and stability of enterogastrone powder. It has been found that a 15 mg-per-kg dose of a typical preparation of enterogastrone will inhibit gastric secretion by 50 per cent, that the inhibitory activity of preparations of enterogastrone and urogastrone is greater than that of other non-toxic agents at comparable dosage levels, and that the enterogastrone activity of dried hog mucosal extracts is unchanged after 12 months

**On the role of glutamic acid in epilepsy** RALPH W WAGER (introduced by Theodore G Bernthal) *Dept of Physiology, Medical College of the State of South Carolina*. Approximately sixty epileptics classified clinically and electroencephalographically as essential or cryptogenic and limited in age from 16 to 40 were placed on a thirty-day regimen of 1(+) glutamic acid, 3 grams t i d. Voluntarily reported apparent beneficial responses constituted the criterion for the formation of Group 1. Those of whom no such voluntary reports were received formed Group 2. Group 3 was a control group composed of every third epileptic and was not initially examined by the Rorschach technique. Chance permitted several of Group 3 to be in each of Groups 1 and 2. The practice effect on the Rorschach ten card procedure was thus controlled.

Subsequent administration of 1(+) glutamic acid to some and of pyrrolidone carboxylic acid to others permits the observations. Rorschach psychograms indicate an increase in number of responses, widened interests, and greater intellectual acuity in almost all Groups 1 and 2. The frequency of clinical seizures was not materially influenced. Electroencephalographically it was not unusual to observe an increase in recorded definition of photic drive responses, and an equally noticeable removal or reduction in the recorded post-ictal psychomotor period.

Use of a placebo for a succeeding thirty-day period permitted a retroversion in psychogram and, in several cases, a return of dysrhythmia disturbing the electroencephalographic recording of the light flicker as well as a noticeable reappearance of the post-ictal psychomotor activity.

The suggestion is offered that analeptic activity observed by others to be possessed by glutamic acid and not attributed to acidosis, may be explained by these findings.

**Further studies on the treatment of experimental renal hypertension with renal extract fractions** G E WAKERLIN, WAYNE DONALDSON (by invitation), OLIVER KAMM, H MINATOYA (by invitation), T LEFCO (by invitation), and JOHN MARSHALL (by invitation) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago and Research Labs, Parke, Davis and Company, Detroit*. Following earlier reports by our group of the antihypertensive effect of daily intramuscular injections of crude hog renal extracts for four to six months in renal hypertensive dogs (*Fed Proc* 5 108, 1946, *Spec Pub N Y Acad Sc* 3 117, 1946), we have continued work aimed at the fractionation, purification, and identification of the active principle of the crude extracts, as well as its mechanism of action. To date a total of twenty five extract fractions have been studied for antihypertensive potency. Six of these have proved definitely active but different lots of presumably the same fraction have varied considerably in potency. We have found one-kidney hypertensive dogs somewhat more responsive to treatment than two kidney (bilaterally constricted) dogs and early renal hypertension more amenable to treatment than late hypertension, although very satisfactory responses have been obtained in long-standing hypertension with sufficiently potent extract fractions. Most of our observations indicate no correlation between the renin content of our extract fractions and their antihypertensive potency or between the antirenin serum titres and the antihypertensive responses of our dogs. However, some other immunologic response may be involved.

As part of our continuing effort to separate and purify the antihypertensive renal principle, we have recently completed a course of treatment in one hypertensive dog with crude dog renal extract prepared from non-renin or low-renin kidneys approximately three months after contralateral renal artery constriction (*Fed Proc* 5 108, 1946). No antihypertensive effect was observed. *[This work was aided by grants from the John and Mary R Markle Foundation and the United States Navy]*

**Further observations on the prophylaxis of experimental renal hypertension with renal extracts** G E WAKERLIN, H MINATOYA (by invitation), T LEFCO (by invitation), JOHN MARSHALL (by invitation) and RUFUS WALKER (by invitation) *Dept of Physiology, Univ of Illinois College of Medicine, Chicago*. We have previously reported successful prophylaxis against experimental renal hypertension in dogs by means of daily intramuscular injections of crude renal extracts for four to six months, and the eventual development of hypertension in four of the five successfully prophylacticated animals 3½ to 4 years after renal artery constriction. We found no correlation between prophylactic effect and the renin content

of the extracts, the serum antirenin titres, or the plasma renin—hypertensin systems. We now report no correlation between the success or failure of prophylaxis in this group of dogs and the renal renin content and no differences at necropsy.

We also reported other evidence indicating that the prophylactic effect of crude renal extracts may last for many months (3 dogs protected out of 5) (Fed Proc 5:107, 1946). The success or failure of prophylaxis in this group was likewise not correlated with antirenin, and we now report no correlation with renal renin content or necropsy picture.

In further studies to produce maximum prophylaxis, elucidate the mechanism, and separate the active renal principle, we have prepared four renal extract fractions. Six of the twelve animals treated with these fractions were protected against experimental renal hypertension. One of the four fractions studied (all of which showed prophylactic activity) was free of renin. There was no correlation between antirenin titre and prophylactic effect. Comparison with therapeutic effect in established hypertension indicated that prophylaxis is a more sensitive test for the antihypertensive renal principle than therapeutic assay. Additional studies are under way. (*This work was aided by grants from the John and Mary R. Markle Foundation and the United States Navy.*)

**The effects of heating by microwaves on venous return.** K. G. WALKER, U. M. LEDEN (by invitation), F. H. KRUSEN (by invitation) and J. F. HERRICK. *Section on Physiology, Section on Physical Medicine and Division of Experimental Medicine, Mayo Foundation and Mayo Clinic, Rochester, Minnesota.* The effects on venous return of microwaves generated by the cavity magnetron (3,000 megacycles per second) were studied in heparinized dogs under pentobarbital sodium anesthesia by means of the bubble-flow meter. The meter was connected through glass cannulae to the proximal and distal ends of the femoral vein, leaving all collaterals and tributaries undisturbed. The venous return from the leg was measured before, during and after placing the director of the microwaves at a distance of 2 to 5 cm. over the thigh for a period of twenty minutes. Before and after application of the microwaves, the temperature of the skin, subcutaneous tissues and muscles of the thigh was determined. Repeated observations were made on the same animal.

Accompanying the rise in the temperature of the extremity produced by the microwaves, a consistent increase in venous return was produced. Of the nine experiments performed to date, all showed an increase over the control flow, eight showed a greater than 50 per cent increase in venous return and only one showed less than 50 per cent increase. With the gradual return of the temperature of the tissues toward the control level there was a gradual

return of the venous blood flow toward control value. In addition to the increase in venous return and the rise in local temperature, there was a slight rise in general body temperature of the anesthetized animal.

**Determination of regional blood flows.** W. W. WILCOTT and F. VELASQUEZ (introduced by Magnus I. Gregersen). *Dept. of Physiology, College of Physicians and Surgeons, Columbia Univ.* The method is based on an extension of the Stewart's original dilution principle.

Sodium para-aminohippurate (PAH) is injected intravenously at a constant rate in the upper extremity after a preliminary priming dose has been injected to saturate the extracellular space. The plasma concentration of PAH reaches an equilibrium within 60-90 minutes. At this time the rate of injection equals the rate of elimination by the kidney. From the equilibrium concentration and the known rate of injection it is then possible, as was independently observed by Earle and Berliner (1946), to calculate the total renal plasma flow. Blood samples taken by venous catheter between the renal and hepatic veins then give the dilution ratio which is the resultant of the admixture of a continuous stream of known flow at zero concentration from the kidneys with an unknown flow at the equilibrium concentration from the common iliacs. By a simple calculation the latter flow can be determined. Similarly the total portal and hepatic flow can be determined by withdrawing a sample between the heart and hepatic veins. A third sample from the superior vena cava will have a higher concentration than the equilibrium value because of the continuous addition of PAH, to this portion of the total venous return. This permits an estimate of the flow through the head and upper extremities. Preliminary observations on dogs will be presented to support the principle of the method. (*Aided by a grant from the Baruch Committee for Physical Medicine to Columbia University.*)

**The effect of desoxycorticosterone acetate and a low K diet on the action potentials induced in rat muscle by indirect stimulation.** SHEPPARD M. WALKER. *Dept. of Physiology, Washington Univ. School of Medicine, St. Louis.* Immature male rats were placed on a low K diet and injected with 2 mg. of desoxycorticosterone acetate daily for 3 to 8 days. The animals were anesthetized with ether and prepared for indirect stimulation of the gastrocnemius muscle. The nerve was stimulated with brief shocks, 3 to 4 times threshold strength. Leads to the amplifier and cathode ray oscillograph were arranged to make possible the recording of action potentials either from the nerve or from the muscle.

An initial large action potential and several subsequent smaller action potentials were recorded from the muscle when a single indirect stimulus



was delivered after a rest period. Repetition persisted for 50 to 75 msec and the discharges were frequently synchronous. The time intervals between the synchronized repetitive discharges became progressively longer. Usually the spike height diminished abruptly toward the end of a repetitive burst without altering the established rhythm. The repetitive muscle spikes were abolished or reduced in size and number by 3 to 6 shocks, at 1 per sec, though the large initial action potentials were unchanged. Following a brief period of rest, repetition could be again induced with a single stimulus. The nerve showed single action potentials following single stimuli and never gave evidence of repetitive discharges, even at high amplification.

The results show that the repetitive discharges originate distal to the point of entrance of the nerve into the muscle. The occurrence of synchronous repetitive discharges suggests that some of the muscle units may function as pacemakers.

**The effect of pitressin on the excretion of chloride and water in the human.** STANLEY L. WALLACE (by invitation), EDWARDS C. WHATLEY (by invitation), GEORGE A. ANDERSON (by invitation) and J. MAXWELL LITTLE. *Dept. of Physiology and Pharmacology and Dept. of Internal Medicine, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.* Twenty-eight patients were hydrated by drinking 400 ml/hr of water from 9 A.M. to 5 P.M. Ten units pitressin were given at 3 P.M., a control urine sample being collected the preceding hour and experimental samples for each of the two following hours. The experiment was repeated at 3 P.M. the following day without special hydration, serum chloride concentration was determined at this time. The urinary volume, specific gravity and chloride concentration were determined.

No relationship existed between serum chloride concentration and control urinary chloride concentration or excretion nor between hydration state and total control chloride excretion.

In 18 experiments (16 patients) the water excretion was unchanged or increased in the first post-pitressin hour, in 15 of these the urine chloride concentration increased (21%–400%), and in 3 decreased (25%–68%). Pitressin may decrease tubular chloride reabsorption independently of its effect on water reabsorption.

In 37 experiments water excretion decreased in the first post-pitressin hour, in 33 of these the urine chloride concentration increased, in 20 of these the total chloride excretion decreased indicating an obligatory chloride reabsorption despite the specific inhibition of reabsorption by pitressin.

With low control total chloride excretion (maximal control chloride reabsorption) the total chloride excretion following pitressin markedly in-

creased (maximum pitressin inhibition of chloride reabsorption) and the water excretion increased (obligatory). With high control total chloride excretion (minimal chloride reabsorption) the water excretion decreased after pitressin (specific pitressin stimulus to water reabsorption) and the total excretion of chloride decreased (minimal pitressin inhibition, obligatory chloride reabsorption).

**An analysis of the carotid sinus cardiovascular mechanism.** S. C. WANG and HERBERT L. BORISOV (by invitation). *Dept. of Physiology, College of Physicians and Surgeons, Columbia University.*

In dogs anesthetized with nembutal, the carotid sinuses were isolated as cul-de-sacs with nerves intact. For stimulating purposes the sinuses were subjected to rectangular pressure changes recorded with a bellows manometer.

For convenience the carotid sinus response is considered in two parts, the cardiac slowing and the vasomotor depression. Each is analyzed (1) for vagal and sympathetic components, (2) adaptation through the aortic depressor nerve, and (3) degree of bilateral representation.

Maximum vagal slowing of the heart, as much as 60 per cent of the control rate, occurs during the first 15 secs of continued bilateral sinus stimulation. However, during the third 15 sec period this restraining effect has already decreased sufficiently to return the heart rate to within 0 per cent to 20 per cent of the control value. Vagal cardiac restraint, though mediated predominantly through the homolateral side, has a small contralateral component, for on stimulation of one sinus in a chronic sympathectomized dog with homolateral vagus cut, some cardiac slowing occurs. It disappears after section of the contralateral vagus. The decrease in vagal tone during pressure stimulation is largely accounted for by the buffer mechanism of the aortic depressor nerves. When they are excluded the vagal response is prolonged.

The maximum depression of the mean blood pressure obtained following bilateral stimulation was 150 mm Hg. This effect is mainly brought about by sympathetic inhibition. Section of both vagi reduces the fall slightly and makes its onset more gradual. Exclusion of both aortic depressor nerves, however, intensifies the response.

**Production of tremor at rest in the monkey.** A. A. WARD, JR. (by invitation), W. S. McCULLOCH and H. W. MAGOUN. *Dept. of Psychiatry, Univ. of Illinois College of Medicine and Dept. of Anatomy, Northwestern Univ. Medical School.* The relief of involuntary movements in man has been handicapped by uncertainty concerning the involved patho-physiology, and inability to produce such movements readily in animals has, in turn, delayed their experimental study.

An enduring tremor in the monkey, resembling



that of Parkinson's disease, has recently been found to follow appropriately located injury to the brain stem. This tremor, present in extremities, trunk or neck, is alternating in antagonistic muscles at frequencies of 8-10/second. It appears when the animal is quiet and disappears during movement.

Answer to two questions would seem preliminary to its further analysis. What structure initiates the motor activity? What structure normally prevents it or prevents its becoming synchronized and repetitive?

Such tremor developed several days after bilateral lesions which destroyed the ventromedial midbrain and pontile tegmentum, without injury to the corpus striatum, subthalamus or substantia nigra. The red nuclei and brachia conjunctiva were also destroyed, but whether this or the tegmental injury is of greater relevance remains to be determined.

In one monkey, in which tremor predominated on the left, the arm and leg portions of right cortical area 4 were removed. Tremor was only transiently abolished and was unaffected by subsequent removal of right area 6 and destruction of the anterior part of the right ventral thalamic nucleus. Conclusions regarding the motor area are equivocal, for its representation bordering the central sulcus was found intact, but neither area 6 nor the pallidum or cerebellar projection to the frontal cortex appears essential for this tremor.

Calcium ions and the development of hardness in the eggs of speckled trout. A. A. WARREN (by invitation), K. C. FISHER and J. F. MANERY. *Univ. of Toronto, Toronto, Canada*. Fish eggs when first shed into stream water are very readily broken by mechanical pressure, but after some time they are found to have taken in water and become resistant to mechanical pressure.

When speckled trout eggs were perfused with varying concentrations of calcium chloride in distilled water, it was found that a concentration of  $M/40,000$  produced just about maximum hardness. A concentration of  $M/640,000$  calcium chloride produced about the same degree of hardness as perfusion with distilled water, this being less than occurs in stream water.

These observations suggest the importance of calcium in the hardening process. To test the presumption that it is the ionized calcium, a series of experiments was made in which eggs were subjected to solutions all of which contained the same concentration of citrate (which by itself prevented all hardening) but which varied with respect to the total calcium content. With this procedure it is possible to vary the degree of hardness from zero to the maximum.

To be sure that citrate does not have any deleterious effect aside from its ability to decrease the concentration of ionized calcium, several experi-

ments were made in which the calculated concentration of ionized calcium was constant although the ratio of total citrate to total calcium varied greatly. Within  $\pm 3\%$  all of these mixtures produced the same hardness. It is therefore concluded that the chemical changes leading to the development of hardness require ionized calcium and that the degree of hardness attained is a function of the concentration of ionized calcium.

Control of the cardiac output in man. Studies on reactive hyperemia. J. V. WARREN (by invitation) and E. A. STEAD, JR. *Depts. of Medicine, Yale and Duke Medical Schools*. The mechanisms in man which increase the cardiac output above the resting level have not been adequately studied because of the difficulty in making quantitative measurements during exercise. A rapid increase in cardiac output and stroke volume can be obtained by suddenly releasing tourniquets on the thighs which have been inflated to a pressure sufficiently high to occlude the arterial inflow for 15 to 20 minutes. Studies with the catheter technique utilizing the Fick principle demonstrate that the cardiac output per minute approximately doubles. Ballistocardiographic tracings show that the change in stroke volume occurs within one beat after the release of the tourniquets. The atrial pressure remains either unchanged or falls. The right ventricular pressure is not altered. By the use of venous tourniquets to pool blood in the legs it can be shown that the increase in cardiac output occurs before blood entering the legs begins to be returned to the heart.

Under the conditions of these experiments, the sudden opening of a large area of decreased peripheral resistance causes a rise in cardiac output which is not dependent on a rise in atrial pressure.

A comparison of the regeneration products of fibrous insulin with native insulin. DAVID F. WAUGH. *Massachusetts Inst. of Technology, Cambridge, Massachusetts*. Fibrogenesis from corpuscular proteins may involve linking the essentially unaltered units or those partially or completely unfolded (ultimately polypeptide chains). Where regeneration is possible the degree of alteration accompanying fibrogenesis may be estimated.

Completely fibrous insulin may be regenerated by alkali (Federation Proceedings 4, 1945). Recently over 80% by weight has been recovered in crystalline form. The following reveal no significant differences between insulin regenerated by alkali (r-insulin) and native insulin (n-insulin): biological assay (courtesy Armour and Co.), r-insulin 20.2 n-insulin 22.2 I.U. per mg., ultracentrifuge analysis (courtesy Dr. L. Oncley), no demonstrable differences in centrifuge patterns, crystallization, both require similar conditions and yield crystals having similar shapes and double refractions, sensitivity to alkali, r-insulin may be somewhat

less sensitive, labile  $\text{NH}_3$ , considered the same since no demonstrable  $\text{NH}_3$  is liberated on elongation at room temperature, disulfide groups remain unchanged

Products of alkaline regeneration usually contain fibril segments which may carry through crystallizations. These elongate (Federation Proceedings, 1946) in the presence of insulin at ordinary temperatures thus falsely indicating large differences between r-insulin and n-insulin. After careful removal of such segments r-insulin initiates fibrils more rapidly and at lower temperatures than n-insulin thus indicating true structural differences. Liquid  $\text{NH}_3$  regeneration products do not seem to initiate fibrils at  $24^\circ\text{C}$  but show increased fibril formation at  $100^\circ\text{C}$ . Comparison ascribes low temperature fibril initiation found with alkali regenerates to the regenerating process. Those irreversible structural alterations inherent in fibril formation are of smaller magnitude.

#### Repetitive discharge in crustacean axons

JOHN H. WELSH *Biological Labys, Harvard Univ*  
Preparations containing one or two active motor nerve fibers of large diameter are readily obtained from walking legs of Crustacea such as crabs, lobsters and crayfish. When these axons are treated with certain organic compounds (e.g. DDT and its analogs, veratrine, pyrethrins, eserine), known to be highly toxic to Crustacea, they first give prolonged volleys of nerve impulses when stimulated with single brief shocks. As poisoning progresses they become spontaneously active and discharge volleys at regular intervals. Within a volley the rate is at first high and declines in a gradual and regular manner.

Small increases in potassium or decreases in calcium cause an earlier appearance of the repetitive discharge, while an increase in calcium as little as 2 times that of the normal perfusion fluid quickly stabilizes the poisoned axon and results in its behaving like a normal fiber.

Since eserine causes multiple discharge which is prolonged by added acetylcholine as well as potassium an attempt has been made to evaluate the roles of these latter substances in the crustacean axon. Unlike eserine, di-isopropyl fluorophosphate (DFP), at all concentrations which have an effect, tends to produce block only. It is not yet clear what part, if any, acetylcholine may play in the phenomenon of repetitive discharge.

The effect of d-tubocurarine on spontaneous activity of frogs' sartorius muscle aroused by calcium lack. BERNARD F. WENDT (by invitation) and A. R. MCINTYRE *Dept of Physiology and Pharmacology, Univ of Nebraska, College of Medicine, Omaha*. Curarine has been found to be incapable of preventing the spontaneous activity of nerve-muscle preparations caused by lack of calcium in the immersing fluid (Kuffler, *J of Neuro-*

*physiology* 7 17, 1944, Adrian and Gelfan, *J of Physiol* 78 271, 1933).

The experiments here reported have been performed in vitro upon frogs' sartorius muscles and show that d-tubocurarine will entirely suppress the activity of frogs' sartorius muscle caused by exposure of the nerve only to calcium free solutions. When the immersing low calcium fluid is allowed to come in contact with both the nerve and muscle at the distal end of the muscle, d-tubocurarine depresses but does not completely prevent the activity of the muscle. Similar results were obtained when isotonic sodium citrate was used as the immersing fluid. Hence, the spontaneous activity observed in sartorius nerve muscle preparations when the immersing fluid is in contact with both nerve and muscle appears to be caused by (a) discharges over motor nerve fibers, (b) direct effects upon the muscle. D-tubocurarine will suppress (a) but not (b).

Because immersion of the nerve-free end (pelvic) of the sartorius in calcium-free solutions is without obvious effect, it appears to have been assumed that the activity observed following exposure of the distal end of the sartorius to such solutions is mediated through the nerves, but these experiments indicate that the muscle activity is in part due to the effect of calcium lack upon the muscle presumably at the sole plate.

The pepsinogen effect of a pancreozymin concentrate. JULIUS WENGER (by invitation) and HARRY GREENGARD *Dept of Physiology, Northwestern Univ Medical School, Chicago, Illinois*. Previous investigators have obtained evidence indicating that the intravenous injection of crude secretin concentrates will stimulate the peptic cells of the gastric glands, whereas highly purified secretin is ineffective in this regard. It has also been shown that from a crude concentrate a fraction may be separated which stimulates enzyme production by the pancreas. It was of interest to note, therefore, whether the agent concerned, designated pancreozymin, is specific for the pancreas, or whether it is capable of stimulating enzyme production elsewhere in the alimentary tract. Therefore, a series of experiments was performed on two dogs with vagotomized gastric pouches, in which gastric juice secreted in response to a small and constant amount of histamine, injected at regular intervals, was collected every ten minutes and analyzed for its free acid and pepsin content. When the secretory rate was brisk and constant and the enzyme concentration minimal (in sixty to ninety minutes) the animals were given intravenously two cc of saline, and thirty to sixty minutes thereafter they received 25 mgms of a pancreozymin concentrate in two cc of slightly acidified water, the concentrate had been previously shown to be potent in stimulating enzyme

production by the pancreas, and to contain no demonstrable amounts of secretin, cholecystokinin, or vasodepressors. The results showed no appreciable effect on volume or free HCl output as a result of either the saline or pancreozymin injection, however, the latter caused within five to fifteen minutes, a significant increase in pepsin concentration. Apparently the concentrate employed has a rather cyanescent but definite pepsinogenic effect, which accounts for the results obtained by other workers, and either the term "pancreozymin" is a misnomer, in the sense that it connotes a restriction of its action to the pancreas, or else there is an associated substance present in the concentrate which manifests an analogous action on the gastric glands.

**Sundry changes in physiology of cerebral cortex following rapid injection of sodium cyanide.** M. D. WHEATLEY (by invitation) and W. S. McCULLOCH, *Dept. of Psychiatry, Univ. of Illinois College of Medicine.* The effect of intravenous sodium cyanide (dose, in mg/kg, injected during seven seconds) on the glass electropotential ( $H^+$ ), noble metal potential (O/R), oxygen tension (O) and activity of exposed cortex (ECG) and the electrocardiogram (EKG), were recorded simultaneously in cats under dihydro erythroidine hydrobromide, artificially ventilated.

All doses gave flattening of ECG and vagal slowing of the heart. 1) 0.1 to 0.4 decreased ( $H^+$ ) and increased (O) for less than a minute. 2) 0.3 to 0.7 gave the above changes, then, for 5 to 40 minutes, increased ( $H^+$ ) and decreased (O) with secondary slowing of the heart. 3) 0.6 to 1.2 gave the same as 2) except that the heart, after 20 to 70 minutes of block and anoxic changes, returned before the ECG when ( $H^+$ ) decreased and (O) increased beyond control values. 4) 1.0 to 1.6 gave the same as 3) except that the ECG never returned and (O) fell suddenly from a high value when edema occluded circulation at the tentorial margin.

All (O/R) changes were referable to change of ( $H^+$ ) and to the circulation, indicating that the (O/R) system communicating with the noble-metal electrode was not cyanide sensitive.

Except for obscuration by decreased circulation due to action of cyanide on the heart, it appears that decrease or absence of cortical activity permitted (O) to rise and ( $H^+$ ) to fall.

Some immediate responses involved in increased arterial pressure. NORMAN C. WHEELER (by invitation), JOHN W. REMINGTON, and W. F. HAMILTON, *Dept. of Physiology, Univ. of Georgia School of Medicine, Augusta, Georgia.* By means of a recently described method the stroke volume, ventricular work and total peripheral resistance were calculated from successive optically recorded pressure pulses. An increase in arterial pressure may be due to an increase in peripheral resistance,

or in blood flow. It tends to curtail the stroke volume, as does myocardial failure, while stimulation of the heart muscle tends to increase the stroke volume. The responses of the cardiovascular system to conventional experiments which raise the blood pressure are analyzed with the above possibilities in mind.

Epinephrine, given intravenously in the doses we have used, caused a great increase in the peripheral resistance and curtailed both stroke volume and ventricular work, in spite of the myocardial stimulation due to the drug. During the succeeding depressor phase the peripheral resistance was lower than normal and the stroke volume higher.

Ephedrine, in our experiments, produced a pressure rise which was due to an increase in stroke volume and cardiac work, with no immediate rise in peripheral resistance, while Priscol produced a rise in blood pressure in spite of reduced peripheral resistance, by means of a marked increase in stroke volume and cardiac work.

Occlusion of the abdominal aorta at the diaphragm increased the peripheral resistance in all cases. In some experiments the stroke volume and ventricular work decreased, in some there was an increase in the ventricular work with a small or negligible decrease in the stroke volume. [This investigation was aided by a grant from Life Insurance Medical Research Fund.]

**Electrical conductivity method for cardiac output.** H. L. WHITE, *Dept. of Physiology, Washington Univ. School of Medicine, St. Louis.* G. N. STEWART's principle of following changes in electrical conductivity of arterial blood on rapid intravenous injection of measured hypertonic salt solution as a measure of cardiac output has been applied to intact animals by constructing conductivity cells small enough to be inserted into an artery. The cells have been either concentric needle electrodes or two fine platinum wires imbedded in plastic insulator and introduced as a stylette. Current source is 70,000 cycles, bridge imbalance is recorded photographically by deflection of a slowly moving spot on a cathode ray oscillograph screen. Calibration is accomplished by titrating a blood sample with the 5 per cent sodium chloride solution used for injection. Cardiac output in dogs under sodium pentobarbital has ranged from 2 to 5 liters/min./M. Fastest circulation time from jugular vein to femoral artery has been 5 to 9 seconds, fastest total circulation time from left ventricle to left ventricle (designated by break in descending curve) has been 7 to 11 seconds. Repeated determinations can be made at short intervals. The method is applicable to man. Rectification of current should permit registration with a sensitive galvanometer or ink-writer. On direct comparisons the method has given values from 0 to 40 per cent higher than Fick values. Electrode troubles and technical difficulties

in calibration have not yet been entirely eliminated, nor has a possible correction factor for salt loss on passage through lungs been established

**Subthalamic lesion in the primate** JOHN R. WHITTIER (by invitation) and FRED A. METTLER *Dept of Neurology, College of Physicians and Surgeons, Columbia Univ* A recent review of the clinical literature by one of the authors (J. R. W.) clearly indicates that in all cases in which the sole lesion is in the subthalamic nucleus the patient exhibits the symptom of hemiballism contralaterally (The possibility that subthalamic lesions may exist in asymptomatic patients whose brains have not been examined cannot be excluded) Hemiballism may also appear without demonstrable pathology of the subthalamic nucleus In such cases its occurrence may possibly be explained on the basis of interruption of afferent or efferent paths of the nucleus

In order to examine the circumstances surrounding the appearance of the symptom, a series of rhesus monkeys is being subjected to stereotaxic lesions of the subthalamic nucleus The number of verified placements is still small In no case thus far has typical hemiballism resulted, although the results suggest that in the rhesus monkey such lesions may produce a unilateral hyperkinesia

In addition to amplification of the information at hand, the circumstances which remain to be investigated are (1) effect of size and type of lesion, (2) position of lesions within the nucleus, (3) significance of involvement of neighboring structures, and (4) the effects of combining other lesions with those of this nucleus

**Comparison of the anti-ulcer activity of enterogastrone and urinary antihelones** ARNE N. WICK (by invitation), FRANCES PAULS (by invitation), ALICE JEAN IRISH (by invitation), and EATON M. MACKAY *Scripps Metabolic Clinic, La Jolla, Calif* Following ligation of the pylorus in the fasted rat ulceration of the gastric rumen occurs Under standard conditions this preparation may be used for measuring anti-ulcer activity A comparison of the activity of two antihelones prepared from human urine—urogastrone and a preparation adsorbed on charcoal and eluted with acetone—with enterogastrone shows that the latter has relatively little anti-ulcer activity Both of the urinary products have comparable activity, purified preparations given intraperitoneally being active in doses of 20 mg/kg while enterogastrone has slight activity at doses 50 times as large The urinary antihelones may also be given intravenously but enterogastrone is too toxic to administer by this route

The active agent in the urinary preparations is nondialyzable and is resistant to the action of pepsin and a stronger proteolytic enzyme ("lethozyme") of marine origin under conditions which lead to the complete destruction of enterogastrone

The "charcoal-acetone process" anti-ulcer factor has been isolated from the urine of all persons examined except those suffering from peptic ulcer Ulcer patients excrete little or none of this anti-ulcer material in their urine

**The effects of carbon dioxide on insulin convulsions and brain potential** G. C. WICKWIRE and RUTH KROUSE (introduced by W. E. Burge) *Dept of Physiology, Univ of Illinois, Urbana* A small goldfish was placed in a horizontal glass tube of water with platinum disk electrodes 6 cm in diameter at the ends of the tube The electrodes were connected by wire with a moderately sensitive galvanometer

It is known that the head of a normal active fish is electropositive with respect to the tail Insulin added to the water caused increased excitability and convulsions In 15 tests an average rise was observed from 0.15 microamperes under normal conditions to 0.5 microamperes during insulin convulsions In advanced stages of insulin shock and inactivity the current decreased to zero

It has been shown that administration of carbon dioxide decreases the positive scalp potential or the negative brain potential of dogs (Anesthesia and Analgesia, Nov-Dec, 1936) Tests in which the goldfish were given carbon dioxide and insulin simultaneously showed no increase in activity and likewise no increase in flow of current

It is suggested that the excess carbon dioxide prevents the hyperexcitability by lowering the negative brain potential

**The influence of prolonged vasoconstriction on the transition from impending to irreversible hemorrhagic shock** HAROLD C. WIGGERS, FRANK ROEMHILD (by invitation), HAROLD GOLDBERG (by invitation) and RAYMOND C. INGRAHAM *College of Medicine, Univ of Illinois, Chicago, Illinois* The temporary blocking of all sympathetic mechanisms, including the partial state of vasoconstriction prevailing in normal resting conditions, was shown to improve the survival rate in animals subjected to 90 minutes of hemorrhagic-hypotension at 35-38 mm of Hg In order to demonstrate more conclusively the deleterious influence of the continuation of intense vasoconstriction during the *impending shock state*, the following experiments were conducted

A graded dose of dibenamine was sought which would prevent the occurrence of excessive compensatory vasoconstriction which is ordinarily invoked following severe hemorrhages Then, after bleeding the untreated animals and allowing the *impending shock state* induced to progress unaltered for 30 minutes, 2 to 4 mg/kg doses of the drug were injected slowly by vein An effective antivasoconstrictor action was presumed to have occurred within the following 15 minutes Thus it was possible to improve the blood flow to such organs as the kidneys, liver and intestines under the pre-

valuing low blood pressures for the last half of the hemorrhagic-hypotension period

The survival rate in the experiments completed as this goes to press is 80 per cent as compared with a 30 per cent recovery rate in the control series. Apparently, therefore, the abolition of severe vasoconstriction in the middle of the hypotension period delays the onset of irreversible shock which usually occurs at this time in untreated animals.

**Acetylcholine in the objective determination of circulation time.** M. WILBURN, J. SCHLICHTEN, M. GROSSMAN and F. CISNEROS<sup>1</sup> (introduced by L. N. Katz). *Cardiovascular Dept., Research Inst., Michael Reese Hospital, Chicago, Illinois.* Employing the onset of asystole as the endpoint for the determination of circulation time, acetylcholine (2½-25 mg.) was injected rapidly into the foreleg vein of 12 trained unanesthetized normal dogs. Arterial pressures and electrocardiograms were recorded continuously before, during and after the administration of the drug. Results revealed the circulation time to range between 4 and 9.5 seconds. The affected endorgan was the sinoauricular node or the auriculoventricular node. The duration of asystole varied from 1 to 5 seconds. An associated transient reduction in blood pressure occurred, apparently due to the combination of asystole and peripheral vasodilatation.

Fractionation of the vascular bed involved was performed in 120 tests in 6 pentobarbital anesthetized dogs by direct injection of 2.5 mg. of acetylcholine into the large vessels of the heart. The times from injection at the mentioned site until the onset of asystole are given below.

Site of injection	Circulation time (seconds)
Superior vena cava	5-11
Main pulmonary artery	3-5
Left ventricular cavity	2
Root of aorta	1

Injection high in the ascending aorta, the transverse arch or descending aorta produced no cardiac slowing. Bilateral vagotomy did not influence circulation time, auricular fibrillation tended to prolong it.

**Turnover rate of sodium in the aqueous humor of the eye measured by radiosodium Na<sup>24</sup>.** WALTER S. WILDE, ROY O. SCHOLZ (by invitation), and DEAN B. COWIE (by invitation). *Depts. of Embryology, Baltimore, of Terrestrial Magnetism, Washington, Carnegie Inst. of Washington, and Dept. of Ophthalmology, Johns Hopkins Univ.* The rate of accumulation of tracer sodium Na<sup>24</sup> in the

aqueous humor is  $dA'/dt = r(P'/P) - r(A'/A)$ , where  $r$  = moles of inherent or body sodium which enter or leave a gram of aqueous per minute,  $P'/P$  is the proportion of entering sodium which is tracer, and  $A'/A$  is the proportion of sodium leaving the aqueous which is tracer. Immediately after intravenous injection the concentration  $P'$  of tracer presented to the aqueous barrier may be (a) identical to that of the plasma and thus follow a typical time concentration or disappearance curve. For guinea pigs we may substitute for  $P'$  the integral of McReel, Gellhorn and Flexner (*J. Biol. Chem.* 153: 83). It is also possible that  $P'$  corresponds more to (b) the instantaneous average value of tracer in interstitial fluid everywhere during the passage of tracer from the plasma. An integral is derived and substituted for this condition. For condition (a) the final integral is  $(1 - A'/A'_{eq}) = (1 + L)e^{-kt} - Le^{-bt}$ , for (b),  $(1 - A'/A'_{eq}) = (1 - M)e^{-kt} + Me^{-bt}$ , where  $A'/A'_{eq}$  = the fraction toward equilibrium attained by the tracer in the aqueous at time  $t$ ,  $k = r/A$  = turnover rate of inherent Na in a gram of aqueous,  $b$  = rate at which Na<sup>24</sup> leaves the plasma,  $L$  and  $M$  are constants. Only form (a) fits 18 experimental points with  $k = 0.016$  turnover per minute.

**Pressures produced in the respiratory tract of anesthetized patients during spontaneous, controlled or artificial respiration.** ROSALINE L. WILHELM (by invitation), WARREN E. GILSON (by invitation), and O. SIDNEY ORTH. *Depts. of Anesthesiology, Medicine and Pharmacology, State of Wisconsin General Hospital and Univ. of Wisconsin Medical School, Madison.* In controlled respiration no spontaneous respiratory movements occur since the anesthetist deliberately increases the minute respiratory volume and reduces the tension of carbon dioxide in the blood below the concentration necessary to stimulate the patient's respiratory center. Continued ventilation permits coordination and regulation of the respiratory movements with the surgeon's operative manipulations.

Pressures so produced in the respiratory passages have been determined and compared with those occurring during spontaneous breathing and in artificial respiration. Closed absorption anesthesia technique was employed with a five liter rubber bag as the reservoir. After oral endotracheal intubation a sterilized No. 10 French ureteral catheter was inserted 35 to 40 cm. through the trachea until resistance was just avoided. The proximal end was attached to a mercury or optical membrane manometer to record intrabronchiolar pressure. A manometer connected with a tube from the mouth registered oral pressures. Quite unexpectedly readings from each type of manometer agreed to within one mm. Hg, in which scale all data is given. Types of respiration and extent of bag filling are tabulated.

<sup>1</sup> Dazian Fellow

These clinical results are substantially equivalent to previous data obtained from dogs

Type of respiration	Oral pressure	Broncholar pressure
Spontaneous without mask on face	No fluctuation	+4
Spontaneous $\bar{o}$ endo tube obstructed	+5 to -8	+6 to -8
Spontaneous + 5L bag just distended	+10	+12
Controlled, bag half filled	+14	+14 to +2
Controlled + 5L bag just distended	+18 to +9	+19 to +12
Neff Lindor Kreiselman bellows	+16 to 0	+13 to 0
E & J Respirator (suck and blow)	+12 to -8	+12 to -8
Silvester manual method	+3	+4 to -2

**Studies on the mechanism of action of veratrine upon the neuromuscular system** J H WILLS *Dept of Pharmacology, Univ of Tennessee, Memphis, Tenn* Veratrine has been found to inhibit both the non-specific cholinesterase of dog serum and the specific one of frog brain (see also Nachmansohn and Schneemann, *J Biol Chem* 159 239, 1945) The effect on the brain esterase was less powerful than that on the serum enzyme

The effect of veratrine upon the isolated sciatic-gastrocnemius preparation of the frog was not enhanced, however, by physostigmine, morphine or caffeine Indeed, these three drugs blocked the typical action of veratrine without affecting significantly the form of the muscle twitch in response to a single nerve volley It appears, therefore, that veratrine does not act through the acetylcholine mechanism but may affect some collaterally-linked system Further studies of the mechanism of action of veratrine are under way

**Determination of serum antiprotease** BETTY WILSON (by invitation) and A J GLAZKO *Dept of Biochemistry, Emory Univ Medical School, Emory Univ, Georgia* A procedure has been devised for the determination of serum antiprotease which has given consistently reproducible results in our hands It has also been applied to the assay of trypsin-inhibitor isolated from soy meal The test is based on the highest dilution of serum or trypsin inhibitor solution required to prevent the lysis of a standard fibrin clot by an enzyme ("fibrinolysin" or "plasmin") found in globulin fraction III-3 from human blood The dry powdered preparation was found to be a convenient source of rotease which retained its activity for long periods of time

The unit of enzyme activity was taken as that concentration of globulin fraction III-3 which would lyse a standard fibrin clot in 7.5 minutes at 38°C following a 30 minute preliminary incubation of the enzyme solution alone Various dilutions of serum were then mixed with one unit of enzyme

and incubated for 30 minutes at 38°C The residual enzyme activity was tested by adding fibrinogen and thrombin to produce a clot, and all tubes were examined after 15 minutes for the first changes in gel structure of the clots This was found to be a more reliable endpoint under the conditions of the test than observations for complete lysis

The antiprotease method has been used to establish the normal blood levels in different species of animals, as well as in man It is being applied to a study of the effect of the adrenal cortex on serum antiprotease, and also to variations of antiprotease in certain clinical conditions [*Aided by a grant from the Life Insurance Medical Research Fund*]

**The effect of low thiamine intake on the oxygen required by women to perform work** MARJORIE WILSON (by invitation), W W TUTTLE and KATE DAUM (by invitation) *Depts of Physiology and Nutrition, State Univ of Iowa, Iowa City* A group of 12 women ate a standard diet containing all nutritional requirements except thiamine The diet did not contain more than 0.13 mg thiamine per day For 6 subjects the diet was supplemented with an adequate amount of thiamine (10 mg) The oxygen required by the low thiamine group to perform 1250 kg work was compared with that required by the control group to perform an equal amount of work The work was measured by an electromagnetic break bicycle ergometer The oxygen used was measured by a modified Benedict-Roth apparatus

Data were collected bi-weekly for a period of 6 weeks to establish an individual standard oxygen requirement Data were collected for a 6 week experimental period

The data show that the oxygen required to perform the specified amount of work by an individual in the low thiamine group is significantly greater than her requirement during a period of adequate intake Conversely, those individuals eating the supplemented diet show a marked decrease in oxygen need under the same work conditions This decreased oxygen requirement has been demonstrated to be the result of training

**A study of the relative potencies of six antihistaminic compounds** CHARLES A WINTER, *Merck Inst for Therapeutic Research, Rahway, N J* Antihistaminic activity has been directly compared by performing parallel experiments on each compound as follows Experiment I Intravenous histamine, 0.5 mg/kg, was lethal to all guinea pigs not protected by antihistaminic drug A determination was made of the lowest dose of drug which would protect the animals The potency of Neoantergan as shown by this test was remarkable, as little as 10 micrograms/kg of body weight protected 100% of the animals Experiment II Guinea pigs exposed to histamine aerosol were removed from the aerosol chamber before death,

and animals were selected for testing antihistaminic drugs which proved on repeated tests to be especially sensitive to histamine administered by this method. Determination was made of the lowest dose of antihistaminic drug which would prevent manifestations of asthma. The same animals were used for testing all the drugs. Under the conditions of this experiment, 100 micrograms/kg of Neoantergan was effective in 100% of the animals. Experiment III. Histamine in concentration of  $2 \times 10^{-7}$  resulted in contraction of the isolated guinea pig ileum. A comparison was made of the degree of inhibition obtained with various antihistaminic drugs present in concentration of  $2 \times 10^{-3}$  when the histamine was added. In all three experiments, the descending order of potency of the six compounds was essentially the same, namely, Neoantergan, Pyribenzamine, 3015 R P, 3277 R P, Benadryl, and Hetramine. It does not necessarily follow that clinical anti-allergic efficacy will be found to parallel antihistaminic potency in all cases.

The relative importance of dietary sodium chloride and water in cardiac edema. A. V. WOLF, D. E. LESTER (by invitation), L. W. GORHAM (by invitation), and H. H. SHULTZ (by invitation), *Albany Medical College and Albany Hospital, Albany, N. Y.* It is now generally recognized that marked restriction of sodium chloride intake is essential in the successful treatment of cardiac edema, and further that water restriction in this condition is practically and theoretically of little value. Whether water should be forced or permitted *ad libitum* is still an undecided question. The following study was undertaken in an endeavor to shed some light on this problem.

Edematous patients on low (0.5 to 1.5 g NaCl) and medium (over 3 g NaCl) daily salt intakes were studied at different levels of water ingestion. As far as the removal of edema was concerned, there was no advantage observed in forcing fluids over allowing patients to take what water they desired.

Observations thus far made on edematous cardiac patients taking a low salt diet do not show that sodium or chloride is excreted at a rate proportional either to water intake or urinary water output. The excretion rate of these ions is more closely related to their load in the body at the time when the low salt intake regimen is started.

Use of the Valsalva maneuver to increase man's tolerance to positive acceleration. E. H. WOOD, *Acceleration Lab. and Section on Physiology, Mayo Clinic and Foundation, Rochester, Minnesota.* Procedures which increase arterial pressure at heart level during exposure to acceleration increase man's g tolerance. Immediately after a Valsalva of 10 or more seconds arterial pressure is decreased for 1 to 2 seconds and then is increased

above the control level for a period of 5 to 10 seconds. A maneuver (M2) has been developed which utilizes this hypertensive period to increase g tolerance.

The maneuver is performed, with the thorax in the inspiratory position and the glottis open, by blowing against a closed manometer system so as to maintain intrapulmonary pressure at 40-60 mm Hg for 10 seconds immediately before g exposure. In a study of 23 subjects under positive acceleration it was found that the usual physiologic sequence of an initial period of progressive failure followed by a period of compensation was reversed by the maneuver. The subjects were in their best physiologic condition during the first 5 seconds of the exposure when the induced increase in blood pressure was at its maximum. A period of progressive failure then occurred which was usually at its maximum toward the end of a 15 second exposure. Thus, the average protection afforded the ear opacity was  $2.0 \pm 0.14$  g for 5 second exposures and  $1.1 \pm 0.1$  g for 10 second exposures to sustained accelerations. The average protection against visual symptoms was  $1.3 \pm 0.1$  g when 15 second exposures to maximum g were used.

Some effects of di-isopropyl fluorophosphate (DFP) and fluoride ion on frog sciatic nerve. J. WALTER WOODBURY (by invitation), LOWELL A. WOODBURY (by invitation), and JAMES E. P. TOMAN, *Dept. of Physiology, Univ. of Utah School of Medicine, Salt Lake City, Utah.* Crescitelli *et al.* (*J. Neurophysiol.* 9:241, 1946) observed that blocking of nerve conduction by brief immersion in DFP solution was rapidly reversed in air. In the present study, conduction recovered spontaneously without removal of the nerve from the DFP solution provided the volume of solution was small. In addition, incubation of small volumes of DFP solution with nerve resulted in a loss of blocking potency when tested on assay nerves.

Liberation of fluoride ion from DFP by nerve, as described for other tissues by Mazur (*J. Biol. Chem.* 164:271, 1946), could account for the observation of Bullock *et al.* (*J. Neurophysiol.* 9:253, 1941) that conduction block produced by DFP in invertebrate nerve becomes less reversible when immersion time is prolonged. In the present study, it was observed that an initial DFP conduction block and subsequent complete recovery were later followed by a progressive and irreversible failure in conduction. The time course of this secondary failure was reproducible by immersion of nerve in the same molar concentration of sodium fluoride solution as of DFP solution. In contrast to primary

<sup>1</sup> Standard error of the mean  $n = 23$ .

<sup>2</sup> Assisted by grants in aid of research from the U. S. Public Health Service and the University of Utah School of Medicine Research Fund.



DFP block, both secondary DFP block and fluoride block were irreversible and could be accelerated by increasing the frequency of nerve stimulation

These results in conjunction with other evidence (Toman, *et al*, these Proceedings) suggest that DFP may block nerve conduction in two ways (1) an early, reversible, nonspecific action of DFP upon threshold, and (2) a later, irreversible action of liberated fluoride ion upon the recovery process

**Energy requirements for the electrical production of seizures**<sup>1</sup> LOWELL A. WOODBURY and C. A. SWINYARD (introduced by James E. P. Toman) *Depts of Physiology and Anatomy, Univ of Utah School of Medicine, Salt Lake City, Utah* Current and energy values for the electrical production of threshold seizures in albino rats were determined as functions of the following stimulus parameters

(1) *Duration of unidirectional rectangular pulses* The threshold peak current decreased and energy increased when pulse durations were varied from 0.05 to 4.5 msec

(2) *Frequency of unidirectional rectangular pulses* The threshold peak current was a minimum at 300 pulses/second. Energy increased with frequency over the range 10 to 1000 pulses/second

(3) *Frequency of alternating sine wave current* The threshold current and energy were minimal at 120 cycles/second. The energy required at this frequency was 42% greater and the average current 14 times greater than for 0.5 msec rectangular pulses at the same frequency. The energy required at 120 cycles/second was only 53% of that at 60 cycles/second, the conventional stimulus used in electroshock therapy

The results illustrate the relative advantage of brief unidirectional pulses over alternating current, as a means of producing convulsions, thereby confirming Liberson (Yale J Biol Med 17: 572, 1945). However, contrary to Liberson, no energy minima were found to exist in the useful range of parameters for unidirectional pulse stimulation

**Cortical origin of the pyramidal tract as defined by antidromic volleys from the medullary pyramid** CLINTON N. WOOLSEY and HSIANG-TUNG CHANG (by invitation) *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore 5, Md* The cortical origin of fibers traversing the medullary pyramid has been defined in rabbit, cat and monkey by stimulating the pyramid electrically and recording oscillographically the cortical responses set up by the antidromic volleys. These responses are initially surface positive and in the cat and monkey consist of a fast brief wave, corresponding to a conduction velocity of approximately 100 meters per second, followed by a more complex

slow wave. In the monkey the amplitude of the fast wave is about twice that of the slow wave while in the cat the slow wave is more than twice as large as the fast. In the rabbit only the slow wave was found. On the assumption that the form of the response is determined by activity in fibers of different sizes and conduction velocities, there is an apparent correlation between the form of the response and the fiber constituents of the pyramids as described for these three species by Lassch.

The region of cortex in which the antidromic response occurs is similar in the three species. It includes Brodmann's areas, 6, 4, 3, 1, 2, 5 and 7 in the monkey and the homologous areas in cat and rabbit.

In the monkey both components of the response are best developed in area 4 but they are almost as large in the postcentral gyrus. In the cat responses are greatest in the Betz cell area.

Afferent responses were avoided by stimulating at a frequency too rapid for thalamic transmission.

**Distribution of cortical potentials evoked by electrical stimulation of dorsal roots in *Macaca mulatta*** C. N. WOOLSEY, H.-T. CHING (by invitation) and P. BARD *Dept of Physiology, Johns Hopkins Univ, School of Medicine, Baltimore 5, Md* In an earlier study the pattern of tactile representation in the postcentral gyrus was analyzed in terms of dorsal roots with the aid of Sherrington's dermatomal maps of the monkey. In the present study that analysis has been confirmed in its essential features, but in addition two new sets of facts have appeared.

1. Besides the postcentral responses which reflect the dermatomal sequence, other postcentral potentials occur which can be accounted for satisfactorily on the assumption that they are derived from proprioceptive afferents in the roots stimulated. Thus when the dorsal root of S1 was excited potentials were recorded not only near the gyrus cinguli in the cortical area for tactile representation of the skin supplied by that root, but a separate group of responses also occurred in the sensory area for the hallux. These responses could have resulted from stimulation of afferents entering S1 from the muscles of the hallux.

2. Dorsal root stimulation, unlike tactile stimulation alone, also evokes potentials in the motor cortex precentrally. The distributions of the precentral responses for various roots supplying the leg suggest that afferent impulses terminate in a definite way in relation to the pattern of representation in the motor area.

**The renal clearance of essential amino acids** LEWEL D. WRIGHT, HORACE F. RUSSO (by invitation), HELEN R. SKEGGS (by invitation), GRACE A. SHANER (by invitation) and KARL H. BEYER *Dept of Pharmacology, Medical Research Division, Sharp and Dohme, Inc, Glenolden, Penna* Micro

<sup>1</sup> Assisted by grants in aid of research from the U. S. Public Health Service and from the University of Utah Research Fund.



biological methods have been used in our evaluation of the renal clearances of essential amino acids in dogs. These methods have the advantage of being based on the physiologic specificity of individual amino acids rather than on chemical reactivity that may be common to more than one amino acid or similar type of compound.

The amino acids histidine, isoleucine, leucine, methionine, phenylalanine, threonine, tryptophane and valine were completely reabsorbed by the kidney tubules at all blood levels studied. In contrast, at plasma levels 5 to 10 times that of the fasting condition the maximal tubular reabsorptive capacity for arginine and lysine was exceeded. Tm values of about 11 and 13 mgm. per minute respectively were obtained for arginine and lysine.

In studies designed to determine whether two amino acids may compete for a functionally common tubular reabsorptive mechanism it was confirmed (Pitts, R. F., *Am J Physiol* 140: 535, 1944) that the coadministration of glycine could inhibit partially the reabsorption of arginine. Similarly, we have found that the amino acid pairs leucine and isoleucine and arginine and histidine compete for reabsorption by the tubules.

**Measurements of blood pressure in the mouse with special reference to age.** CHENTZE HSIANG WU (by invitation), and M. B. VISSCHER, *Dept of Physiology, Univ of Minnesota Medical School, Minneapolis*. The plethysmographic method has been adapted to measure the arterial pressure of the mouse. The occlusion cuff placed at the tail root consists of a latex tube supported by a glass chamber about 8 mm. wide. The width and elastic characteristics of the cuff tubing have determining effects upon the occlusion pressure in this system. The water plethysmograph enclosing the remainder of the tail is in communication with a 0.6 mm. bore side tube. The cuff pressure at which outward movement of fluid in the capillary tube occurred has been checked against direct measurements of carotid artery pressure in nembutalized mice. In 13 observations the cuff pressure agreed with the carotid artery mean pressure with an average difference of +2 per cent and a range of +10 to -11 per cent. Repeated measurements by the plethysmographic method on groups of unanesthetized mice showed reproducibility. Excitement of the animal must be avoided. The mouse is confined in a moulded wire mesh holder fitting the head and body, with the head end darkened.

Studies on mice of various ages of the C<sub>3</sub>H strain have shown a tendency for the blood pressure to rise with age. The average reading for 19 mice of 2.5 and 5 months was 111 mm. Hg, ranging between 95 to 138, 14 mice 13-14 months averaged 136 mm. Hg, the range being 114-165, 13 animals between 31-32 months averaged 151 mm. Hg, the range being 138-164.

**Effect of cerebral concussion upon the threshold of electrically induced convulsions.** H. T. WYCKS (by invitation), M. MARKS (by invitation) and E. A. SPIEGEL, *Dept of Exp Neurology, Temple Univ Medical School, Philadelphia, Pa*. Using the method of electrical stimulation with the skull intact (Spiegel, J. Lab and Clin Med 22: 1274, 1937) the effect of concussive blows upon the convulsive reactivity was studied in 15 rats and 22 cats. In the majority of the animals, 11 rats and 12 cats, a decrease of the convulsive reactivity was observed, in some animals within a few minutes following the blow, while in others the decrease of excitability developed on the next day. It lasted up to several weeks, when the general behavior and reflex activity of the animals failed to reveal other abnormalities. Sometimes there was only a decrease of the duration of the convulsions, while a change of threshold was absent or inconclusive. In 2 rats and 2 cats a decrease of the convulsion threshold appeared in the first days following the blow. In 2 cats there was initially no change of threshold, however, after several days the threshold decreased below the preconcussion value. Increased convulsive reactivity could also develop after a period of decreased reactivity. These changes could be observed for several weeks. Spontaneous convulsions did not appear except immediately following the blow. [Aided by a grant from the John and Mary R. Markle Foundation.]

**Regulation of heart rate after chronic sino-aortic denervation.** W. B. YOUNG, H. V. GOOD (by invitation) and A. F. HEWITT (by invitation), *Dept of Physiology, Univ of Oregon Medical School*. Unanesthetized dogs having had both carotid sinuses either denervated or excised and both vagi cut either near the base of the skull or in the midcervical region show the high cardio-accelerator tonus which is characteristic of experimental neurogenic hypertension. Following intravenous injection of 1½ units of pitressin in such animals the cardio-accelerator tonus is suspended so that a considerable cardiac slowing occurs. Similar doses of pitressin produce negligible effects on the rate of the denervated heart.

Injection of various vasoconstrictor compounds results in a striking decrease in heart rate in unanesthetized rabbits having had both aortic depressor nerves sectioned and both carotid sinuses excised. The vagi probably provide an afferent pathway from the aortic arch.

The high cardio-accelerator tonus in unanesthetized dogs with sino-aortic zones denervated is not decreased by allowing them to breathe 100% oxygen, and it is not increased by moderate hypoxia. Cardiac slowing following injection of pitressin occurs whether the dog is breathing air or 100% oxygen.

The cardiac slowing produced in dogs by injecting

pitressin is unaffected by abdominal sympathectomy, or by low thoracic transection of the spinal cord, or by removal of both oculi

At present the possibility remains that thoracic nerves provide an afferent pathway for depressor reflexes. If not, it would seem likely that cephalic mechanisms are involved in initiating cardiac slowing during a severe rise in pressure in the cerebral blood vessels. Perhaps the mechanism is the same as that involved when the extravascular intracranial pressure is increased [*Aided by a grant from the John and Mary R. Markle Foundation*]

**Hepato-renal factors in circulatory homeostasis**  
**XIII Effects of acute renal ischemia on the renal vaso-excitator mechanisms** B. W. ZWEIFACH, S. BAEZ (by invitation) and EPHRAIM SHORR, *Dept. of Medicine, Cornell Univ. Medical College and The New York Hospital, New York City*. In hypertensive animals (dogs, rats) a vaso-excitator principle (VEM) is formed by kidney despite its adequate oxygenation, whereas normal kidneys produce VEM only anaerobically. The time relationships of the transformation of this "Pasteur reaction" by which a normally anaerobic process occurs under aerobic conditions were studied by observing the effects of acute renal ischemia on the *in vivo* and *in vitro* formation of VEM. Occlusion of the renal circulation in rats for 10-20 minutes was followed by a transient hyper-reactivity to epinephrine of the terminal blood vessels in the meso-appendix. With more prolonged renal ischemia (20-90 minutes) persistent hyper-reactivity developed, the vessels becoming 200-300 times more responsive to epinephrine for at least 60 minutes, the period of observation. With renal ischemia lasting 150-240 minutes there occurred a gradual deterioration of the VEM mechanism, little or no vascular hyper-reactivity resulting.

These *in vivo* changes were shown to be related to specific alterations in the mechanisms for VEM formation and inactivation, by means of *in vitro* incubation studies of ischemic kidneys. Kidney slices, ischemic for 10-30 minutes before incubation, resembled normal kidney, forming VEM only anaerobically. After 40-90 minutes of ischemia, kidney slices produced VEM even under aerobic conditions. With more prolonged ischemia (120 minutes or longer) there was a progressive impair-

ment in the ability of the kidney to form VEM both aerobically and anaerobically. These changes in VEM formation following prolonged ischemia were accompanied by a progressive deterioration of the renal mechanism for VEM inactivation [*Aided by grants from the Josiah Macy, Jr. Foundation and the Eli Lilly Co.*]

**Hepato-renal factors in circulatory homeostasis**  
**XI A vaso-excitator principle in the blood of hypertensive dogs** B. W. ZWEIFACH, EPHRAIM SHORR and S. BAEZ (by invitation), *Dept. of Medicine, Cornell Univ. Medical College and The New York Hospital, New York City*. The presence of a blood borne vaso-excitator principle (VEM) in experimental hypertension (Goldblatt clamp) has been demonstrated by the intravenous injection of 0.5 cc of heparinized whole blood, 2-10 minutes after its withdrawal, into a normal rat for bioassay. The detection and quantitation of VEM was based on the development of a hyper-reactivity to epinephrine in the terminal arterioles and precapillaries of the meso-appendix of the test rat. Control blood samples from 60 normal dogs were well tolerated by the rats and produced no changes in the epinephrine reactivity of the peripheral blood vessel.

VEM appeared in the renal vein blood within 30 minutes after partial constriction of the renal artery by a Goldblatt clamp. Blood from dogs made hypertensive by this procedure continued to show pronounced VEM activity throughout the period during which the blood pressure was progressively rising. VEM disappeared from the blood when the blood pressure had become stabilized in the hypertensive range in dogs with 2 renal clamps or with 1 kidney clamped and the other removed, or when it had fallen to normal levels in dogs with 1 kidney clamped and the other intact. In the last group, clamping of the second kidney resulted in the reappearance of VEM during the subsequent rise in blood pressure. On stabilization of the blood pressure at new hypertensive levels, VEM again disappeared.

Renin and a vaso-constrictor, assumed to be hypertensin, have also been demonstrated during the acute phase of renal hypertension. VEM however differs in certain vascular effects from both [*Aided by grants from the Josiah Macy, Jr. Foundation and the Eli Lilly Co.*]

## THE AMERICAN SOCIETY FOR BIOLOGICAL CHEMISTS

## THIRTY-EIGHTH ANNUAL MEETING

Chicago, Ill, May 18, 19, 20, 21, 22, 1947

(For possible corrections in any of the following abstracts see the next issue)

**Determination of phenolsulfatase activity**  
L D ABBOTT, JR (introduced by J C Forbes)  
*Dept of Biochemistry, Medical College of Virginia, Richmond* Phenolsulfatase activity was measured colorimetrically by the amount of phenol liberated in a specified time at the optimum pH and temperature of the enzyme using potassium phenylsulfate as the substrate. Curves showing the effect of pH, substrate concentration, temperature, incubation time and enzyme concentration on the activity of the phenolsulfatase of takadiastase will be presented. Optimum activity was obtained at 50°C with 0.02 M potassium phenylsulfate in 0.2 M sodium acetate acetic acid buffer (pH 6.2 at 25°C). The method was found suitable for the determination of phenolsulfatase activity in small amounts of material with comparatively short incubation periods. Phenolsulfatase activity of a number of enzyme preparations was compared. No activity was noted in human serum with this method at either 37.5° or 50°C, for incubation periods up to 18 hours.

**Vitamin C aerosol for inhalation therapy of the lungs**  
HAROLD A ABRAMSON, M D *From the Medical Services and Labs of the Mt Sinai Hospital, New York City* Diverse properties of medical significance have been ascribed to Vitamin C. Amongst these are antiviral activity, enzyme inactivation, formation of cement substance in connective tissue and acceleration of fibrosis in the therapy of tuberculosis. It seemed important therefore, to explore the feasibility of employing Vitamin C as an aerosol for topical therapy in suppurative and other infectious pulmonary diseases, not only for its own action but also for synergistic characteristics in connection with antibiotics like penicillin, streptomycin and hydrogen peroxide.

**Methods** Aerosols were generated with the DeVilbiss No. 40 or 640 (nasal tips) nebulizers. Oxygen at 5 to 10 liters per minute was used with the patients inspiring the aerosol directly without rebreathing.

**Stability** 5% to 20% sodium ascorbate solution can be readily nebulized by oxygen without appreciable decomposition in the nebulizer itself. Using a modification of the centrifugal condenser of Abramson and Demerec, the nebulized sodium ascorbate was collected in more dilute solution. Some evidence of decomposition was observed in the condensate but sufficient sodium ascorbate is

delivered to the patient by this technique without due loss, to make the procedure a practical therapeutic operation. After thirty minutes of nebulization the concentration of sodium ascorbate in the nebulizer increases appreciably because of more rapid evaporation of the solvent and probably because of the anticatalyst action of the concentrated ascorbate solution.

**Clinical trials** Preliminary experiments show that 15% sodium ascorbate may be inhaled for 15 minutes as sodium ascorbate aerosols without irritation by patients with severe asthma. A ten per cent solution of sodium ascorbate may be given six times daily without irritation. Higher concentrations can probably be used. Present clinical trials include tuberculous and non-tuberculous suppurative pulmonary disease and virus infections.

**The tryptophane requirement of the infant**  
ANTHONY A ALBANESE, L EMMETT HOLT, JR, VIRGINIA IRBY (by invitation), SELMA E SNYDERMAN (by invitation) and MARILYN LEIN (by invitation) *New York Univ College of Medicine* Although it has long been known that on a body weight basis the protein requirements of the infant are approximately 5 times greater than those of the adult, it is as yet not known whether the high nitrogen requirements of the infants are created by an increased need of all of the amino acids or by a limiting effect caused by higher demands of the growing organism for one or more of the amino acids. In order to secure information on this point, three infants were fed tryptophane deficient and tryptophane supplemented-tryptophane deficient diets at the rate of 100 calories per kilogram body weight per day and having the following percentage caloric distributions: protein, 14, fats, 36, carbohydrate, 50. The necessary vitamins were supplied as Brewers' yeast, ascorbic acid and oleum percomorphum. On the basis of changes in rate of weight gain and nitrogen retention induced by fractional supplementation of the tryptophane deficient diet, it could be estimated that the infant requires approximately 30 mg of l(-) tryptophane per kilo of body weight per day. This value is approximately 5 times the adult tryptophane requirement previously reported by us and suggests that the high protein need of the infant is predicated in part by the tryptophane requirement.

Measurements of the blood proteins during the

experiment disclosed that within 10 days, a tryptophane deficient diet caused an appreciable hypoproteinemia which is reflected for the most part in a decreased albumin level. This result is to be contrasted with the failure of the plasma proteins of the adult male to reflect a tryptophane deficiency of 6 weeks duration.

These findings cannot but impress one of the relatively greater biological sensitivity of the infant to dietary privations and of the desirability of determining the nutritional requirements of the infant directly rather than by deductions from results of adult human or rat experiments.

**The determination of nitrogen balance indexes of protein hydrolysates in dogs** J B ALLISON, R D SEELEY (by invitation) and F P FERGUSON (by invitation) *Bureau of Biological Research, Rutgers Univ*. The relationship between absorbed nitrogen (AN) and urine nitrogen (UN) is described by the following equation

$$UN = (1-K) (AN) + UN_0 \quad (1)$$

where  $UN_0$  is the excretion of urine nitrogen on a protein-free diet and  $K$  is the nitrogen balance index of the hydrolysate.  $UN_0$  is a function of the magnitude of the protein stores, decreasing in value as the stores decrease. When  $K$  and  $AN$  are constant equation (1) becomes

$$UN = UN_0 + C \quad (2)$$

which describes a straight line with a slope of unity. This linear relationship holds for data obtained while feeding hydrolysates either orally or intravenously provided  $UN_0$  is greater than 80 mg N/day/kilo of body weight. When  $UN_0$  is less than this, the nitrogen balance index is a variable, increasing as  $UN_0$  decreases.  $UN_0$  can be determined while feeding dogs sufficient protein with a nitrogen balance index of unity to maintain nitrogen equilibrium. By so doing the requirements of the equation can be satisfied for intravenous feeding without depleting the dog in nitrogen.

The average nitrogen balance index of a fibrin hydrolysate was essentially independent of the rate of infusion from 0.5 to 7.0 mg N/min/kilo. Higher levels of plasma amino nitrogen were obtained, however, at the faster rates of infusion and the excretion of urine amino nitrogen increased correspondingly. The addition of glucose to the hydrolysate did not alter the nitrogen balance index provided sufficient calories were given orally.

**Effect of calcium on the inhibition of the succinic oxidase system by  $\alpha$ -tocopheryl phosphate** STANLEY R AMES (introduced by Philip L Harris) *From the Labs of Distillation Products, Inc., Rochester, N Y*. Attention has been focused on  $\alpha$ -tocopheryl phosphate ( $\alpha$ -TPh) as an inhibitor of succinic dehydrogenase, particularly as it relates to muscle dystrophy and congestive heart

failure. The inhibition of the succinic oxidase system by  $\alpha$ -TPh can be diminished by adding calcium chloride, the extent of inhibition being inversely proportional to the concentration of added calcium chloride. A reaction between calcium chloride and  $\alpha$ -TPh occurs in aqueous solution at a molar ratio of two or more to one which completely removes  $\alpha$ -TPh from solution. The addition of  $l(+)$ -glutamic acid to a succinic oxidase system strongly inhibited by  $\alpha$ -TPh, partially relieves the inhibition but the addition of  $d(-)$ -glutamic acid is without effect. The addition of coenzyme I to a succinic oxidase system slightly inhibited by  $\alpha$ -TPh results in a pronounced increase in the extent of inhibition.

The following mechanism is proposed to explain in part the inhibition of the succinic oxidase system by  $\alpha$ -TPh. When  $\alpha$ -TPh is added *in vitro* it combines with calcium which is an integral part of the succinic dehydrogenase assay method. The calcium concentration is decreased below the critical level necessary to activate coenzyme I nucleotidase and the coenzyme I-linked malate system functions as a result. Oxalacetate produced in the malate system inhibits succinic dehydrogenase with the resultant overall effect of an inhibition of the succinic oxidase system on the addition of  $\alpha$ -TPh.

This mechanism may explain the abnormally high oxygen uptakes observed in dystrophic muscle slices.

**The effect of alloxan on the level of serum amylase of the rat** MARIE A ANDERSON and C JELLEFF CARR *Depts of Medicine and Pharmacology, School of Medicine, Univ of Maryland, and the Clinical Labs, Univ Hospital*. The amylase in the blood serum of rats was determined by a saccharometric method using beta amylose as the substrate before and at intervals following the intraperitoneal administration of alloxan. The normal values ranged between 1000 units and 2000 units compared to 40 to 150 units in the serum of man by the same method. The response to alloxan was variable and could not be correlated with the severity of the hyperglycemia. A number of the animals showed a marked fall in the serum amylase. An attempt has been made to correlate these changes with pathological changes in the pancreas.

**Enzymic hydrolysis of phytin by pure bacterial cultures** JAMES C ANDREWS and ENRIQUE HERRARTE (by invitation) *Dept of Biological Chemistry and Nutrition, School of Medicine, Univ of North Carolina, Chapel Hill, N C*. The nutritional availability of phytin phosphorus is limited by its very slight degree of hydrolysis in the human gastro-intestinal tract. Tests were therefore made of the ability of pure cultures of a variety of organisms to effect this hydrolysis. Commercial phytin was converted into the hexa

barium salt and twice reprecipitated as such before treatment with an equivalent amount of sulfuric acid. The phytic acid was neutralized to give the sodium salt. Subcultures of a number of common organisms found in the intestinal tract, in water, and in soil were standardized nephelometrically and incubated with the sodium phytate for 24 hours at 37°C. The resulting inorganic phosphate was determined by Gomori's method.

The following organisms gave negative results: *Alk. fecalis*, *B. subtilis*, *Bru. abortus*, *E. typhosa*, *Proteus vulgaris*, *Pseud. aeruginosa*, *Sal. aertrycke*, *Sal. enteritidis*, *Sal. supester*, *Sarcina lutea*, *Serratia marcescens*, *Staph. aureus*, *Strep. fecalis*.

The following produced a slight degree of hydrolysis (1 to 4%): *Pseud. fluorescens*, *S. dysenteriae*, *S. paratyphosa*, *Staph. citreus*, *Vib. metchnikowii*.

The following organisms effected a greater degree of hydrolysis: *A. aerogenes*, 18%, *E. coli*, 13%, *S. sonnei*, 13%.

Thus, of the organisms tested, appreciable hydrolysis was observed only with certain of the intestinal bacteria, but of these none could come in contact with ingested phytin high enough in the tract to permit absorption of the resulting phosphate.

**Turnover of bone measured with radiophosphorus.** W. D. ARNSTRONG, *Dept. of Physiological Chemistry, Univ. of Minnesota, Minneapolis, Minnesota*. It has been demonstrated that the specific activity of the urine of mature rats remains unchanged from the 10th to at least the 14th week after administration of radiophosphorus, from which result it can be concluded that the specific activity of the plasma inorganic phosphorus also does not change during the same period. By the 11th week the specific activity of bone exceeds that of the urine and the exchange of radiophosphorus by bone with the plasma after this period is not affected by changing specific activity of the latter, as is the case early after the administration of the radioisotope.

Eleven weeks after the administration of radiophosphorus to eight mature rats urine was collected and the right fore limbs were removed. Three weeks later the animals were sacrificed. The average specific activity of the left humeri was 9.2 less than that of the right humeri. It is concluded that the complete turnover of the bone of the humeri of rats due to exchange plus bone regeneration would require at least 230 days.

**Effect of protein deficient diets on the skeleton of the mature rat.** W. D. ARNSTRONG and HAYDEE LSTREMLER (by invitation), *Dept. of Physiological Chemistry, Univ. of Minnesota, Minneapolis, Minnesota*. Diets containing 18.0 (Group 1), 13.5 (Group 2), 9.0 (Group 3) and 4.5 (Group 4) per

cent protein as lactalbumin were fed to groups of 23 male rats (average initial weight 262 grams) for 30 days in such manner that the average daily food consumption of the animals in the several groups was equal. The average weight changes of the members of the four groups were respectively 53.8, 39.7, 23.2 and minus 13.9 grams in spite of the fact that the calorie intake of each of the four groups was equal. The dry, fat-free and ash weights of the humeri of the animals of Group 2 were not significantly different from those of Group 1. However, the results obtained with Groups 3 and 4 were significantly lower than those obtained with Group 1, showing that protein depletion results in bone atrophy.

**Action of choline and fat on the formation of liver phospholipids.** CAMILLO ARTOM and W. E. CORNATZER (by invitation), *Dept. of Biochemistry, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.* Male rats (100-110 grams) were maintained for seven days on a diet containing casein 5 parts, dextrin 42, sucrose 42, Crisco 4, cod liver oil 1, salt mixture 4, ruffex 2, and B vitamins. In each experiment four rats were given the following by stomach tube: Rat A, water; Rat B, choline HCl, 30 mg; Rat C, oil, 2.2 cc and choline HCl, 30 mg; Rat D, oil, 2.2 cc. All rats were then injected with a solution of phosphate containing radioactive phosphorus and killed after a certain time interval (3 to 24 hours).

In the liver lipides of Rats B, receiving choline, both the total radioactivity and the specific activity of the phosphorus were higher than in Rats A. When, in addition to choline, fat also was administered (Rats C), there was a further increase in the total radioactivity, usually also in the specific activity values. In Rats D, to which fat, but no choline was given, values were approximately the same as in Rats A.

These results parallel those of similar experiments on the formation of phospholipids in the small intestine (Artom, C., and Cornatzer, W. E., *J. Biol. Chem.* 165: 393 (1946)). In both liver and intestine of rats on a low fat, low protein diet, choline stimulates lipid phosphorylation, but the highest degree of stimulation is observed when single doses of choline and fat are given simultaneously. It may also be of interest to compare our present findings with those of previous investigations in which the effects of changes in the amounts of dietary choline and fat on liver phospholipids were studied (e.g., Fishman, W. H., and Artom, C., *J. Biol. Chem.* 164: 307 (1946)). [Aided by a grant from the John and Mary R. Markle Foundation.]

**A new enzymatic phosphate transfer.** B. AXELROD (introduced by A. K. Balls), *Enzyme Research Lab., Bureau of Agricultural and Industrial*

*Chemistry Agricultural Research Administration, USDA, Albany, California* There are two recognized ways in which organic phosphate linkages can arise enzymatically, (a) reversal of a hydrolytic or phosphorolytic reaction and (b) transfer of phosphate from a high energy phosphate to an acceptor

A new mode of phosphate esterification is indicated by the behavior of an acid phosphatase preparation obtained from orange juice (*J Biol Chem* 167 57 (1947)) When this preparation acts upon p-nitrophenyl phosphate in the presence of methanol, as much as 60 per cent of the hydrolyzed phosphate fails to appear as inorganic phosphate In the absence of methanol, equivalent amounts of nitrophenol and inorganic phosphate are liberated The enzyme preparation cannot transfer inorganic phosphate to methanol or p-nitrophenol

Monophenyl phosphate and phenolphthalein phosphate can also serve as phosphate donors A number of alcohols can replace methanol In general, primary alcohols are best Tertiary butyl alcohol is unsuitable Some polyhydroxy compounds including glycerol and mannitol are effective, but sucrose, alpha-methyl glucoside and inositol are not

From the behavior of the enzyme preparations on purification and in the presence of inhibitors it would appear that the transfer reaction is catalyzed by the phosphatase However, extracts from plants other than citrus have been obtained which possess phosphatase activity but are either incapable of carrying out the transfer reaction or do so less efficiently than the orange preparation

**On the inhibition of enzymes by ionizing radiations** E S GUZMAN BARRON, SHERMAN DICKMAN (by invitation), and T P SINGER (by invitation) *From the Metallurgical Lab, and the Chemical Division of the Dept of Medicine, The Univ of Chicago, Chicago, Illinois* It is generally accepted that the primary process on the radiation of water is the splitting into H atoms and OH radicals In the presence of dissolved  $O_2$  there is also formation of  $H_2O_2$  Ionizing radiations may then inhibit sulfhydryl enzymes through oxidation of the -SH groups by OH radicals and  $H_2O_2$  Phosphoglyceraldehyde dehydrogenase was irradiated with increasing doses of x-rays from 25 r to 500 r The enzyme was half-inhibited with 200 r and almost complete inhibition occurred with 500 r On addition of glutathione there was reactivation of the enzyme Previous addition of glutathione reduced inhibition Inhibition was also obtained with  $\gamma$  particles (polonium),  $\beta$  ( $Sn^{99}$ ) and  $\lambda$  (radium) radiations Similar inhibitions were found with other sulfhydryl enzymes, namely adenosinetriphosphatase, urease and succinodehydrogenase Inhibition of urease by  $\lambda$  radiations could not be released by glutathione However,

when the sulfhydryl groups of urease were protected from oxidation by mercaptide formation (addition of p-ClHg benzoic acid)  $\lambda$  radiations had no effect on the activity of urease On inhibitions produced by  $\gamma$  particles on phosphoglyceraldehyde dehydrogenase, the presence of catalase reduced the inhibition By this device it was found that about half of the total inhibition might be due to  $H_2O_2$  formed during irradiation Inhibitions produced by  $\beta$  radiations were not reversed on addition of glutathione It was, however, almost completely eliminated by previous addition of catalase That inhibitions were due to the action of OH radicals and not to direct "hit" of the rays on the enzyme molecule were demonstrated by increasing enzyme concentration Inhibition diminished and even disappeared in agreement with the results reported by Dale<sup>1</sup>

**Dextrose nitrogen ratios in pyridoxine deficiency** PAUL BARTLETT (by invitation) and OLIVER H GAEBLER *Henry Ford Hospital, Detroit* Since the capacity of rat tissues to catalyze transaminase activity is reduced in pyridoxine deficiency it seemed of interest to determine D N ratios in phlorrhizized dogs on a pyridoxine deficient diet This contained vitamin-free casein, 72%, corn oil, 20%, Phillips-Hart salt mixture, 4%, and calcium phosphate, 4%, supplemented with haliver oil, thiamine, riboflavin, niacin, choline, and pantothenic acid

Dog 1 did not become anemic on this diet, but complete incoordination of gait and convulsions occurred after 34 days All symptoms disappeared when pyridoxine was given Beginning on the 18th day of a second depletion, phlorrhizin was administered for 6 days All food was refused during this period On the first 4 days the D N ratios were 3.49, 3.04, 2.70, and 2.79 During the next 2 days 20 mg doses of pyridoxine were given subcutaneously twice daily, and the ratios rose to 3.42 and 3.65

Dog 2 showed a steady fall in hemoglobin despite constant and adequate food consumption On and after the 22nd day 1 gm of desoxyypyridoxine was fed daily without notably accelerating the development of anemia The antivitamin was continued during the 28th to 30th day, while phlorrhizin was given The D N ratios were 2.67, 2.90, and 3.01 During these days the animal refused about half of its food Phlorrhizin was continued for 3 more days, but the antivitamin was stopped and pyridoxine was given The dog resumed eating all of its food and the D N ratios were 3.21, 3.26, and 3.24

**Quantitative fluorescent micromethod for the determination of natural estrogens** ROBERT W BATES and HERMAN COHEN (by invitation) *Bi-*

<sup>1</sup> Dale W N, *Biochem J* 34 1367 (1940)

*ological Labys*, E R Squibb & Sons, New Brunswick, N J The well known qualitative Cuboni test for pregnancy, based on observation of the green fluorescence developed upon heating a urine extract with concentrated  $\text{H}_2\text{SO}_4$ , has been developed to make it quantitative Quantitative readings are obtained only within certain limits of acid concentration and heating Linear quantitative results are obtained with 1-10% of estrone using a Klett fluorimeter and a Corning 038 or 306 photocell filter or a Coleman Photofluorometer and a B<sub>1</sub> photocell filter Fluorescent intensities of other steroids relative to estrone are estradiol 100%, estriol, equilin and dihydroequilenin about 50%, pregnanediol, progesterone, testosterone, androstenediol and dehydroisandrosterone less than 5% **PROCEDURE** Carefully pipette the sample in 0.10 to 0.20 ml of ethanol or 0.10 ml of N/1 NaOH into the bottom of a fluorimetric test tube Add 1 ml of 90%  $\text{H}_2\text{SO}_4$  (10 ml  $\text{H}_2\text{O}$  plus 90 ml  $\text{H}_2\text{SO}_4$ , c p) Shake the test tube and place it for 10 minutes in a water bath at 50°C to develop maximum fluorescence After heating, add 6 ml of 65%  $\text{H}_2\text{SO}_4$  (35 ml  $\text{H}_2\text{O}$  plus 65 ml  $\text{H}_2\text{SO}_4$ , c p) to the tube and thoroughly mix with a cork-screw shaped glass rod Read fluorescence on this diluted solution The fluorescence is stable for 24 hours at room temperature Oxidizing agents or dilution with water destroy the fluorescence Toluene, benzene, ethyl ether or ethylene dichloride may also be used as a solvent Aliphatic solvents with three or more carbons in the chain can not be used without evaporation because they yield colored condensation products

**Action of thiocyanates in producing goiter**  
EMIL J BAUMANN and NANNETTE METZGER (by invitation) *From the Laby Division, Montefiore Hospital, New York City* Goiter produced by thiocyanates is explained on the basis (1) that the thyroid filters all halogens from the circulation very effectively but distinguishes between them imperfectly if at all, (2) that thiocyanates are likewise taken up by the thyroid preferentially, a not unexpected finding in view of their position at the end of the Hofmeister series, (3) that in the presence of a large amount of thiocyanate (or any halogen) compared to the small quantity of iodine usually present, iodine will be prevented from being filtered from the blood by the thyroid or be washed out from the gland before its elaboration to thyroxine occurs The effect is similar to a mass action effect

In support of this concept evidence will be presented showing that when relatively large amounts of thiocyanate or of any halogen are given, the thyroid more than any other tissue will take up these anions and (2) if the medication is continued, thyroid hyperplasia and goiter will develop, due we believe to the washing out of iodine

from the body by the mass action of the administered anion Such effects have been prevented by giving additional iodine

**The comparative metabolism of Jaffe reactive substances in the rat** HOWARD H BEARD *Dept of Physiological Chemistry, The Chicago Medical School, Chicago, Illinois* Small, intermediate and very large doses of creatine, creatinine, glyco-  
cyamine, glyco-  
cyamidine, hydantoic acid and hydantoin were administered to 6 groups of rats by intraperitoneal injection and by mouth 50 mg dose, Creatine caused a retention of creatinine, creatinine stimulated creatine and creatinine excretion 150 mg dose, Creatine gave no increase in creatinine excretion, creatinine gave an increase in creatine of 101 mg, hydantoin and glyco-  
cyamidine were transformed into creatine and creatinine and stimulated their excretion, glyco-  
cyamine increased creatinine excretion but not creatine excretion Addition of glycerophosphate with the supplements caused greater increases in muscle creatine than with the supplements alone 125-175 mg daily for 10 days, Increases in creatine excretion ranged from 0 to 251 per cent, in creatinine excretion from 4 to 160 per cent A mutual interconversion of glyco-  
cyamine glyco-  
cyamidine and of hydantoic acid-hydantoin of 1-2 per cent occurred Methylation of the substances to creatine and creatinine was much greater than amination to glyco-  
cyamine and glyco-  
cyamidine All values for creatine and creatinine were true values With the exception of glyco-  
cyamidine, over 90 per cent of these ingested doses disappeared

Two theories of creatine and creatinine formation were suggested

- (1) Amino acids  $\rightarrow$  hydantoic acid  $\rightarrow$  glyco-  
cyamine  
 $\rightarrow$  creatine
- (2) Amino acids  $\rightarrow$  hydantoin  $\rightarrow$  glyco-  
cyamidine  
 $\rightarrow$  creatinine  $\rightarrow$  creatine

the first of which occurs if large doses of supplements are administered while Reaction 2 is considered physiological and much evidence was given to support it

**Some observations upon the nature and distribution of Jaffe reactive material in beef liver** HOWARD H BEARD *Dept of Physiological Chemistry, The Chicago Medical School, Chicago, Illinois* Ground beef liver was extracted twice with 35 per cent dioxane and five times with water at 60°C The nature and distribution of the Jaffe reactive material of these extracts was studied by the use of our specific creatinine enzyme together with the addition of alkaline picrate before and after incubating the samples with HCl The total Jaffe material of 4994 grams of liver was 1810 mg distributed as follows

- (a) extracts of water and dioxane soluble fractions, 638 mg, of which true creatine was 243 mg (38%), true creatinine, 199 mg (31.2%), residual



total Jaffe reactive material, 99 mg (15.5%) and residual preformed Jaffe material, 99.4 mg (15.2%). The ratios were, true creatine, true creatinine residual total and preformed Jaffe, 2.5, 1.9, 1.3 (b) 505 mg of total Jaffe reactive material not extracted from 3000 grams liver tissue insoluble in water and (c) 667 mg of total Jaffe reactive material lost in the technique used, 55.4% of which was accounted for in control experiments.

Since glycoeyamidine and glycoeyamine were destroyed during the study evidence pointed to hydantoin and hydantoic acid as the substances responsible for the total and preformed residual Jaffe reactive material in liver. It was suggested that early in the formation of creatine and creatinine from their precursors in the liver all of these substances may be joined in peptide or other union in the insoluble globulin fractions. This observation, as well as those of Roche, *et al*<sup>1,2</sup> may also indicate that the guanidine and anhydride types of linkage are present in some of the liver proteins.

**Effect of large doses of Jaffe reactive substances upon urinary excretion of nitrogenous constituents.** HOWARD H. BEARD *From the Dept of Physiological Chemistry, The Chicago Medical School, Chicago, Illinois.* Approximately 2750 mg of creatine, creatinine, glycoeyamine, glycoeyamidine, hydantoic acid and hydantoin, was ingested in the drinking water of 6 different groups of rats during a 12 day experimental period. The excretion of total, urea and ammonia nitrogen was determined at 3 day intervals and determinations of the excretion of the other 4 substances made as listed in the previous abstract. About 22% of the ingested nitrogen disappeared after deduction of the control nitrogen which was likewise untraced. Since a decrease of 73% in the average urea nitrogen excretion occurred in the 6 different groups, it was concluded that the liver detoxicated these substances into unknown nitrogenous compounds with a resulting diminution in protein catabolism. The transformation of the 3 pairs of substances into each other was of the same order of magnitude as in the previous study. It was also observed that none of the 6 ingested substances were transformed into urea or ammonia.

**The production of creatine-creatinine destroying enzymes from human urine and gastric juice.** HOWARD H. BEARD *Dept of Physiological Chemistry, The Chicago Medical School, Chicago, Illinois.* When human urine is allowed to stand at room temperature for a few days bacteria are produced on top of the urines and on the sides and bottom of the beaker. After separation from the

urine and incubation with creatine and creatinine these substances were destroyed from 1 to 13 mg per hour from the first through the fifth runs. The enzyme secured from human gastric juice destroyed from 0.7 to 2.7 mg creatinine per hour. Optimum pH for enzyme action was from 7 to 10. The pH of the different solutions usually increased from 7 to 8.8 with the production of urea and ammonia. The creatinine enzymes did not destroy glycoeyamine, glycoeyamidine, (Cf following abstract) hydantoic acid or hydantoin. Further studies are in progress to identify the bacteria responsible for the production of these enzymes.

**The products of proteolysis of some purified proteins.** ANNE BELOFF (by invitation) and CHRISTIAN B. ANFINSEN *Dept of Biological Chemistry, Harvard Medical School.* An investigation has been made of the peptides formed in crystalline trypsin and pepsin proteolysis of the following substrates: crystalline serum albumin and egg albumin, and purified fibrin and  $\gamma$  globulin.

The average number of amino acid residues in the peptide molecule was determined. These determinations were made by analysis of the terminal peptide amino-nitrogen (using the Van Slyke nitrous acid method) and the total amino acid nitrogen liberated by acid hydrolysis of the peptides (using the ninhydrin method). The ratio of these two values determines the average number of amino acids per peptide molecule.

The values obtained with trypsin on (a) serum albumin, (b)  $\gamma$  globulin were 2.5-3.2 and 2.7-3.7, respectively. For pepsin on (a) serum albumin, (b) egg albumin, and (c) fibrin, they were 3-4, 6.7-7, and 3.3-3.8, respectively. It was found that these values showed little variation at any period during digestion. This supports the view of Tiselius and Erickson-Quensel, and others, that the protein molecules are broken down rapidly one after the other to low molecular weight peptides.

Very little free amino acid nitrogen is liberated by crystalline proteolytic enzymes, approximately 1 per cent of the total peptide amino-nitrogen.

To prevent the possible resynthesis of peptides, a digestion system was set up in which the peptides were continuously removed by dialysis from the enzyme-substrate solution. Analysis of these peptides confirmed previous results.

**The specificity of hydantoïnase.** FREDERICK BERNHEIM *Duke Medical School.* The enzyme in the livers of omnivores which hydrolyzes hydantoin will not hydrolyze any of the substituted hydantoin tested. These, kindly supplied by the E. I. Du Pont de Nemours and Co., included the dimethyl, methyl-ethyl, methyl-isobutyl, methyl-n-hexyl, methyl-n-amyl, diisobutyl, 2-ethyl-propyl, and pentamethylene spiro derivatives. The last compound inhibits the hydrolysis of hydantoin in

<sup>1</sup> Roche J. and Blanc Jean G. *Comp rend acad Sci* 210 681, 1940

Roche J., and Vialatte G., *Comp rend soc biol* 137 543, 1943

a concentration of 10 mg/cc whereas the other compounds show only slight inhibitory effects in concentrations of 50 mg/cc. The effectiveness of the pentamethylene derivative is probably due to the pentamethylene ring because metrazol also inhibits at the same concentration.

The selective inhibition of active phosphate bond metabolism in human malignant cells MAURICE M. BLACK (by invitation) and ISRAEL S. KLEINER *New York Medical College and Brooklyn Cancer Inst.* Malignant cells have long been known to exhibit increased aerobic and anaerobic glycolytic activity. Attempts to inhibit the growth of such tissue by the use of inhibitors of glycolysis by other investigators have been indecisive. In view of the importance of the active phosphate bonds in energetic reactions, we have attempted selective energetic inhibition in relation to these bonds.

The inhibitors used were sodium fluoride, iodoacetic acid, and malonic acid. In the doses used, these substances, both singly and in combination, resulted in encouraging therapeutic effects without evidence of appreciable toxicity. The cases studied included acute leukemia, and a diversified group of other malignant tumors. Hematological and clinical remissions were observed in a significant number of leukemias studied. The beneficial results in other types of malignancies included shrinkage of tumor mass, relief of pain, increase in weight and well-being, and definite changes on biopsy.

No definite cures have been obtained. There is evidence that, after one inhibitor has had its effect, accessory pathways of phosphate bond formation develop. These may be inhibited, when known, and when the inhibitor is available, viz. the use of malonate after sodium fluoride and iodoacetic acid have become ineffective. In our studies adaptation to all three seems to be the limiting factor in continued therapeutic effect.

These studies support the concept of specific energetic inhibition of malignant cell metabolism. Continued study of the problem of cell adaptation will be necessary before complete control of such metabolism will be possible. [Aided by grants from the Biochemical Research Fund of the New York Medical College and the Leukemia Research Foundation.]

Diagnostic changes in the reducing power of plasma in malignant neoplasia and therapeutic implications MAURICE M. BLACK (introduced by Israel S. Kleiner) *New York Medical College and Brooklyn Cancer Inst.* Many attempts have been made to demonstrate differential reactions in the serum of patients suffering from neoplastic diseases. Studies of the reducing power of plasma have been suggestive of a diminished reducing power associated with malignant neoplasia.

As our interest lay in evaluating systemic alterations associated with malignancy an attempt was made to devise a method of evaluating such changes.

Determination of the reducing power of plasma (or serum) was made by the use of the redox dyes, brilliant cresyl blue and methylene blue. It was found that plasma of patients with malignant diseases tended to have a lowered reducing power and could be differentiated from normal plasma and from plasma of patients suffering from conditions other than malignancy. Diverse malignant conditions gave varied degrees of alteration of the reducing power which tended to be characteristic. Adequate therapy either x-ray, surgery or chemotherapeutic inhibition, reversed the characteristic alteration of reducing power. Thus the effect of therapy could be followed objectively.

The diagnostic accuracy of this procedure may be illustrated by the following accuracy ratios, controls (normals) 50/50, non malignant diseases 111/120, active malignancies 158/184.

These observations suggested the concept that some of the symptomatology associated with malignancy might be due to the altered enzyme activity as a result of diminished SH potential. Accordingly glutathione was administered intravenously. Chills and rise in temperature were noted, followed rapidly by dramatic relief of pain and general improvement. These results could be repeated and sustained. No effect was noted, however, on the growth rate of the tumor itself. [Aided by grants from the Biochemical Research Fund of the New York Medical College and the Leukemia Research Foundation.]

Influence of sulfhydryl groups on oxygen consumption of tissues in the presence of gold compounds WALTER D. BLOCK, NAOMI GEIB (by invitation) and WILLIAM D. ROBINSON (by invitation) *Dept. of Biological Chemistry and the Rackham Arthritis Research Unit, Medical School, Univ. of Michigan, Ann Arbor.* It has been previously demonstrated that the oxygen consumption of liver and kidney slices from healthy white rats, as measured by the Warburg technique, is decreased by the addition of gold chloride and gold sodium thiosulfate. Because of the ability of the sulfhydryl group to combine in vitro with heavy metals the effect of this group on the oxygen consumption of slices of rat kidney and liver in the presence of gold chloride and gold sodium thiosulfate was studied. The sulfhydryl group was furnished by thiomalic acid and cysteine hydrochloride.  $2 \times 10^{-4}$  molar thiomalic acid decreased the oxygen consumption approximately the same degree as  $2 \times 10^{-4}$  molar gold chloride. When these substances were added together in this molarity there was again essentially the same depression of oxygen uptake. However, when  $2 \times 10^{-4}$  molar thiomalic acid

and  $\frac{1}{100}$  molar gold chloride were added together to tissue slices the oxygen consumption was essentially the same as in the control groups. In contrast the addition of mixtures of either  $\frac{1}{100}$  molar or  $\frac{1}{100}$  molar thiomalic acid and  $\frac{1}{100}$  molar gold sodium thiosulfate resulted in the same depression of oxygen consumption as when  $\frac{1}{100}$  molar gold, sodium thiosulfate was added alone.  $\frac{1}{100}$  molar cysteine hydrochloride added to tissue slices caused no depression of oxygen uptake. The addition of both  $\frac{1}{100}$  molar gold chloride and  $\frac{1}{100}$  molar cysteine hydrochloride resulted in the same degree of depression of oxygen consumption as when  $\frac{1}{100}$  molar gold chloride was added alone.

A colorimetric method for the determination of small amounts of lipid. W. R. BLOOR, *Dept of Biochemistry, School of Medicine, and Dentistry, Univ of Rochester*. The method is based on the measurement of the change in color of Nicloux reagent (a concentrated sulphuric acid solution of dichromate, containing silver) resulting from the oxidation of fatty acid or cholesterol. The change of color is from the bright orange yellow of the acid dichromate to a dark greenish brown, and may be measured in an ordinary photoelectric colorimeter. Better results are obtained by the use of a special type of the instrument in which the light is made to pass through a layer about 4 cm thick instead of the 1.2 cm of the test tube ordinarily used.

The range of measurement of lipid is from 0.2 to 0.8 mgm with the amount of reagent used. Oleic and palmitic acids and cholesterol give parallel curves, the cholesterol being about 10% stronger. The accuracy of the method with reasonable care is about 5%.

The significance of border-line values of serum free cholesterol. By AARON BODANSKY (*From the Chemical Lab, Division of Labs, Hospital for Joint Diseases, New York*). Most reported values do not indicate adequately the constancy of the free cholesterol/total cholesterol ratio in the normal serum. When technical errors are minimized, free cholesterol constitutes probably about 28 to 29 per cent of the total cholesterol of normal human serum. As determined by a procedure to be described, in which technical errors of about 2 per cent are tolerated (involving errors of about 1 per cent in the calculated percentages of free cholesterol), our normal values ranged between 27 and 30 per cent, in about 10,000 determinations we have found only two values of 26 per cent and one of 25 per cent.

Species differences are indicated. Free cholesterol percentages in serum of normal dogs raised in our laboratory were about 2 per cent lower than in human serum.

The equilibrium between the cholesterol fractions is also shifted, but in the opposite direction,

in clinical diabetes, hypertension and certain other conditions. A much larger proportion of the values approach the upper normal limits—even when there is no evidence of organic liver involvement.

Consistent successive values above 30 per cent indicate organic or functional liver injury. Values not higher than 35 per cent are quite consistently found—in absence of obstruction of the bile passages—even in extensive carcinomatosis of the liver.

The magnitude of the relative increase of the serum free cholesterol fraction helps—in connection with other data of serum analysis—in differentiating between various kinds and degrees of experimental and clinical liver injury.

Protection of mice from the lethal action of some bacterial endotoxins by penicillin administered previously. ALDEN K. BOOR, C. PHILLIP MILLER and WALTER D. HAWK (by invitation), *Dept of Medicine, Univ of Chicago*. Previous reports from this laboratory (*Science* 102, 427, 1945 and *Proc Soc Exper Biol and Med* 61, 18, 1946) have described the effect of penicillin on the lethal action of bacterial toxins in experimental animals. A definite degree of protection was afforded by repeated subcutaneous injections of penicillin extending over a 24 hour period beginning about two hours before the administration of sterile endotoxin. This procedure was deemed advantageous because the frequent penicillin injections insured its presence in the blood during most of the period of evident intoxication.

In the present work we have subjected mice to a series of rather massive subcutaneous doses of penicillin in water totaling 12,000 to 20,000 units and then, after a resting period of 10 to 17 hours, administered sterile lysed bacteria intraperitoneally. Despite the fact that detectable penicillin had disappeared from the blood before the time of injection of the endotoxin, a higher survival quota resulted than in control mice given the toxins without the advantage of the previous penicillin treatment.

Other mice were injected with water solutions of penicillin by the peritoneal route, and after 15 to 20 hours had elapsed, injected with the toxic bacterial material. These were found to be protected to an even greater extent than the mice treated with penicillin by subcutaneous injections. The degree of animal protection by the method now presented, when endotoxin administration is delayed several hours after penicillin treatment, is often as high and sometimes higher than by the procedure previously reported.

Homologues of methionine sulfoxide as glutamic acid antimetabolites. ERNEST BORCK (by invitation) and HEINRICH WAELSCH, *Depts of Biochemistry, New York State Psychiatric Inst and Hospital and Columbia Univ, New York*.

The sulfoxide derived from ethionine is ineffective as an antimetabolite against glutamic acid in the metabolism of *Lactobacillus arabinosus* in concentrations at which the sulfoxides derived from methionine or S benzyl homocysteine inhibit bacterial growth completely. In an attempt to elucidate the importance of the S substituents in this reaction the sulfoxides and sulfones derived from n-propyl-, n-butyl-, n-amyl-, n-hexyl-, and n-lauryl-homocysteine were prepared and tested for antimetabolite activity. The propyl sulfoxide was as inactive as the ethyl derivative, but, starting with the butyl homologue, increasing inhibition of bacterial growth was noted with increasing chain length. The inhibition was only partially overcome by glutamine or increased amounts of glutamic acid.

The dissociation constants of the sulfoxides derived from methionine and ethionine were found to be identical, and dissociation was thus excluded as a factor in their strikingly different behavior in the metabolism of the organism.

**Oxidative and non-oxidative transmethylation reactions.** HENRY BORSOOK and JACOB W. DUNNOFF *Wm G Kerckhoff Labs of the Biological Sciences, California Inst of Technology, Pasadena, California*. Two categories of methyl transfer reactions have been demonstrated. One is dependent on oxygen and is inhibited by oxidation inhibitors. Examples in this category are the methylation of guanidoacetic acid by methionine and of nicotinamide by methionine. Choline and betaine are ineffective as direct methyl donors. These reactions have been demonstrated with rat liver slices.

Transmethylations in the second category are independent of oxygen and are not inhibited by oxidation inhibitors. Examples in this category are the methylation of homocysteine, homocystine, or homocysteinethiolactone by either choline or betaine. The rate of methylation by betaine is faster than by choline.

Homogenates of rat liver suspended in buffer solution do not methylate guanidoacetic acid with or without added methionine; they are able to catalyze methionine formation by transmethylation under both aerobic and anaerobic conditions.

**Acceleration of blood coagulation by iodinated trypsin.** DONALD E. BOWMAN *Dept of Biochemistry and Pharmacology, Indiana Univ School of Medicine*. Trypsin which has been allowed to react with sufficient iodine to greatly decrease its hypotensive effect when injected intravenously retains its ability to accelerate the *in vitro* coagulation of the recalcified plasma of normal dogs. Present evidence indicates that the coagulating effect of crude trypsin iodinated under standardized conditions with  $1.5 \times 10^{-3}$  to  $2.0 \times 10^{-3}$  milliequivalents of iodine per milligram of trypsin does not differ greatly from the accelerating effect

of the non-iodinated enzyme. This is consistent with the greater loss in the hypotensive effect than in the proteolytic activity of the enzyme as the result of such iodination.

The trypsin was rather slowly iodinated at pH 7 and at 38°C, avoiding a marked excess of iodine during the period of reaction.

**Further differentiation of bean antitryptic factors.** DONALD E. BOWMAN *Dept of Biochemistry and Pharmacology, Indiana Univ School of Medicine*. Soy bean antitryptic factors may be differentiated from an earlier described antitryptic factor of navy beans. The navy bean antitryptic substance differs from the crystallized soy bean factor in that it can be recovered almost quantitatively from the supernatant solution after being heated in 2.5 per cent trichloroacetic acid. The navy bean factor further differs from the crystallized soy bean antitrypsin in that it is not precipitated in a 0.4 saturated solution of ammonium sulfate. However, it is precipitated in a solution 0.7 saturated with this salt. It is precipitated most readily with alcohol at a higher concentration than that used to precipitate the crystallized soy bean factor.

Crude navy bean preparations are somewhat more active than the crystalline soy bean antitrypsin, especially when the latter was obtained from treated commercial soy bean meal. The activity of this navy bean factor is not diminished by short periods of heating but it is markedly decreased by prolonged boiling.

Aside from differing in solubility in alcohol, this navy bean factor also differs from the soy bean antitryptic fraction which has been referred to as the acetone insoluble factor in that the latter is not precipitated in 10 per cent trichloroacetic acid.

Soy beans also contain an antitryptic fraction similar to this navy bean factor. Crude preparations obtained from soy beans in particular may consist of varying proportions of the various factors unless sufficient precautions are taken.

**A chemical method for the determination of streptomycin in blood.** GEORGE E. BOYER and VIOLA C. JELINEK (by invitation) *Research Labs of Merck and Company, Inc., Rahway, New Jersey*. A method for the determination of streptomycin in blood must be highly sensitive, since level of clinical interest range from 1-50 micrograms per ml. The methods based on the formation of maltol from streptomycin are not sufficiently sensitive.

A fluorometric method is presented which is dependent on the aldehyde group and the strong basic character of the streptomycin molecule. A hydrazone is formed with fluorescent 9-hydrazinoacridine-HCl on standing overnight in a solution at 37°C. Excess reagent and hydrazone carbonyl compounds not removed by extraction are removed by extraction.

tion with benzyl alcohol. The fluorescence of the aqueous solution is measured in a fluorophotometer and is proportional to the streptomycin content.

The sensitivity of this method is from 1-30 micrograms of streptomycin. As a lower limit 0.07 micrograms per ml of streptomycin can be determined provided that 14 ml of solution is available.

The agreement between this fluorometric method and the less sensitive colorimetric methods based on maltol formation is satisfactory.

For the determination of streptomycin in blood, the reaction is applied to a protein-free filtrate prepared with trichloroacetic acid. Correction is made for the small percentage of streptomycin adsorbed on the protein precipitate. Data on specificity, reproducibility, and recovery of streptomycin from blood are presented.

#### Growth requirements of *Clostridium welchii*

M. JOHN BOYD (by invitation), MILAN A. LOGAN, and ALFRED A. TYTELL (by invitation). *Univ of Cincinnati College of Medicine*. *Clostridium welchii* BP6K gives a luxuriant growth on a chemically defined medium which contains amino acids, vitamins, adenine, guanine, uracil, glucose, and salts, of which magnesium and iron are important. Nineteen amino acids are in the medium but only thirteen are actually required by the anaerobe. The nine amino acids essential for the rat and also glutamic acid, tyrosine, arginine, and serine are required. The vitamins added consist of thiamine, niacin, riboflavin, Ca pantothenate, biotin, folic acid and either pyridoxamine or pyridoxal. Pyridoxamine may replace either of the latter two vitamins but it must be used in amounts a thousand fold greater. Uracil when added to the medium accelerates the growth of the organism. The organism grows rapidly and luxuriantly at 45°C. The possible utilization of the organism for amino acid assays is discussed.

**Use of carbon 14 in the study of photosynthesis.** A. H. BROWN (by invitation), E. W. FAGER (by invitation), and H. GAFFRON. *Dept of Chemistry (Fels Fund), Univ of Chicago*. Carbon 14 in the form of carbonate has been fed to unicellular green algae, the uptake of the carbonate being followed manometrically. After rapid killing, the algal material has been separated into various fractions on the basis of solubilities. One of these fractions has been found to have an activity per milligram which is significantly higher than that of any other fraction. This high activity suggests that some of the substances contained in this fraction are involved in the early stages of photosynthesis. This is further supported by the observation that the per cent of the overall uptake of radioactive carbon accounted for by this fraction decreases with an increase in the time of exposure

to light. The properties of the substances contained in this fraction have been investigated.

**Reversible oxygenation of cobaltodihistidine to oxy-bis(cobaltodihistidine), and comparisons with other metal-amino acids, oxyhemoglobin, and oxyhemocyanin.** DEAN BURK, and (by invitation) JOHN HEARON, HILTON LEVI, and ARTHUR L. SCHADE. *National Cancer Inst., National Inst of Health, Bethesda, Maryland, and Oerly Biochemical Research Foundation, New York*. One cobaltous ion and two isoelectric histidine molecules form cobaltodihistidine and two protons reversibly ( $K_{37.5} C_{aq} = 7 \times 10^{-7}$ ,  $\Delta H = 19$  Kcal). One  $O_2$  and two cobaltodihistidine molecules form oxy-bis(cobaltodihistidine) rapidly and reversibly ( $K_{37.5} C_{aq} = 3.1 \times 10^5$  liters<sup>2</sup>/mole<sup>2</sup>,  $\Delta H = -38$  Kcal). Oxy-bis(cobaltodihistidine) reacts slowly and irreversibly with one additional  $O_2$ , without oxidation to cobaltic form. Dry, powdered oxy-bis(cobaltodihistidine) yields 0.0 quantitatively upon acidification. At 0.005M cobalt, and pH 8.0, oxy-bis(cobaltodihistidine), its irreversibly oxygenated product, and cobaltodihistidine, are yellow-brown, pink, and faint pink, respectively, with optical densities 4.5, 0.62, and 0.09 at 4860 Å, where the two last-named show absorption maxima, and cobaltodihistidine anomalous dispersion (Cotton effect).

Reversible oxygenation did not occur with (1) cobaltous complexes of amino acids other than histidine or histidine-derivatives (3-methyl histidine, 1-methyl histidine, carnosine, anserine, aspartylhistidine, histamine), (2) an intermediate cobaltous-(histidine)<sub>2</sub> complex formed at low pH, wherein cobalt coordinated only with the two amino, but no longer the two basic imidazole nitrogens, and (3) histidine complexes with other transition metals ( $Cu^+$ ,  $Cu^{++}$ ,  $Ni^{++}$ ,  $Fe^{++}$ ,  $Mn^{++}$ ). Rapid irreversible oxidation of  $Cu^+$  and  $Fe^{++}$  in the complexes occurred.

Cobaltodihistidine, like hemocyanin, does not combine with  $CO$ , though hemoglobin and myoglobin do. The metal  $O_2$  ratio in oxy-bis(cobaltodihistidine) and oxyhemocyanin is 2:1, compared to 1:1 in oxyhemoglobin and oxymyoglobin. The magnetic moment of cobaltodihistidine, in collaborative experiments with Dr. L. Michaelis, was 4.97 Bohr magnetons, corresponding to 3 unpaired electrons and incomplete quenching of the orbital moment. The paramagnetic cobaltodihistidine, like hemoglobin, became diamagnetic upon reversible oxygenation, and the irreversibly oxygenated product was likewise diamagnetic.

**Polarographic determination of cytochrome c.** CHRISTOPHER CARRUTHERS (introduced by H. A. Mattill). *From the Research Dept of the Barnard Free Skin and Cancer Hospital and the Dept of Anatomy, Washington Univ School of Medicine, St. Louis, Missouri*. A polarographic method for

the determination of cytochrome c in tissues has been developed. The procedure is based upon the property of cytochrome c to give a catalytic wave on the current-voltage curve of a solution of the enzyme in ammonium hydroxide and ammonium chloride containing hexammino cobaltic chloride. Electrophoretically prepared cytochrome c<sup>1</sup> was used as a basis of reference for construction of a calibration curve for analytical purposes.

The cytochrome c is extracted from tissues by the procedure of Rosenthal and Drabkin,<sup>2</sup> and for polarographic analysis the extract is freed of proteins which interfere with the formation of the catalytic wave of cytochrome c by adsorption on aluminum oxide to which cytochrome c and some other proteins are strongly adsorbed. Proteins which are not adsorbed are then washed off the alumina with phosphate buffer of pH 6.8-7.0 and the cytochrome c and other adsorbed proteins are eluted with 2N ammonium hydroxide. After neutralization of the latter in the cold with hydrochloric acid, extracts of heart, skeletal muscle and kidney are ready for polarographic analysis. In the case of liver extracts the cytochrome c must be adsorbed twice on alumina to get rid of all the interfering proteins.

The height of the catalytic wave is sufficient to allow one to determine as little as 1 to 2 micrograms of cytochrome c per ml of solution. The values obtained for mouse and rat tissues by the polarographic method are in agreement with those obtained spectrophotometrically.

The acceleration of enzymatic desamidation of glutamine by certain inorganic anions. CHARLES E. CARTER (by invitation) and JESSE P. GREENSTEIN, *National Cancer Inst., National Inst of Health, Bethesda, Maryland*. The desamidation of glutamine in aqueous extracts of rat liver is accelerated by pyruvate. A similar and more rapid acceleration of enzymatic desamidation is effected by inorganic phosphate, arsenate, sulfate and borate in the absence of added pyruvate. The anion effect is not destroyed by prior dialysis providing the pH of the dialysate is maintained between 7.5-8 during the procedure. In the case of phosphate acceleration of desamidation, no conversion of inorganic to organic phosphate can be demonstrated, and the maximal effective concentration of phosphate for several concentrations of glutamine was found to be 0.03M. The pH optimum of the anion effect occurs at 8.0, the optimum of glutaminase.

The inorganic anion effect is specific for the γ

group of glutamine for isoglutamine is not enzymatically desamidated at a greater rate in the presence of anions effective for glutamine. Chloroacetylglutamine behaves like glutamine but is less rapidly desamidated.

Pyroglutamic acid has been excluded as a product of the anion activated desamidation of glutamine in liver extracts by application of the ninhydrin and chloramine T reactions.

The mechanism of the anion acceleration of desamidation may be due to either the formation of a labile imide ester intermediate of glutamine or an anion activation of glutaminase.

Oxidation of *meso*-inositol by *Acetobacter suboxydans*. H. E. CARTER, R. K. CLARK, JR. (by invitation), EDWIN H. FLYNN (by invitation), BETTY LITTLE (by invitation), and MARY ROBBINS (by invitation), *Division of Biochemistry, Noyes Lab of Chemistry, Urbana, Illinois*. The oxidation of inositol by *Acetobacter suboxydans* has been reported to yield inosose<sup>1</sup> and "diketoinositol."<sup>2</sup> We have made a detailed study of the process using several strains of the organism and following the disappearance of inositol by a yeast assay method. Different strains of the bacterium show considerable variation in their ability to metabolize inositol. With the more active organisms grown on a 2 per cent inositol medium, there is little or no inositol left after 2-3 days. At this point an excellent yield of scyllo-mes inosose can be isolated from the culture medium. If the fermentation is allowed to proceed for longer periods the yield of inosose decreases and fractions are obtained having physical properties similar to those of "diketoinositol." Since these mixtures could not be separated by direct recrystallization they were converted into derivatives by treatment with phenylhydrazine. Extraction of the product with ether removed a dark red component. The residue on crystallization from methanol yielded the phenylhydrazone of inosose and on chromatographing over alumina in methanol-pyridine gave a yellow crystalline product analyzing correctly and giving the proper ultraviolet absorption spectra for the osazone of diketoinositol.

The properties and metabolism of these substances and of related compounds will be discussed. [The authors gratefully acknowledge a grant in support of this work from the Abbott, Eli Lilly, Parke Davis, and Upjohn Companies.]

A study of the yeast fermentation method for the determination of thiamine and pyrimin. W. O. CASTER (by invitation), OLAF MICKELSEN and ANGEL KEYS, *Laby of Physiological Hygiene, Univ. of Minnesota, Minneapolis*. In the macro-

<sup>1</sup> The author is indebted to Dr. Hugo Theorell of the Biochemical Institution of Medical Nobel Institute, Stockholm, Sweden for the sample of electrophoretically prepared cytochrome c.

Rosenthal O. and Drabkin D. L. *J. Biol. Chem.* 149: 437 (1943).

<sup>2</sup> Klayver, A. J. and Boezgaard, A. G. *J. Rec. trav. chim.* 58: 955 (1939).

Pitcher W. H. *Iowa State Coll. J. Sci.* 16: 120 (1941-42).

fermentation method for the determination of thiamine, the relation between  $\text{CO}_2$  production and the concentration of either thiamine or its pyrimidine moiety is not linear even within the limits of concentration routinely used. On a molar basis, these curves are not identical, and when both compounds are added to the same flask the resulting  $\text{CO}_2$  production is not the sum of that expected from the activities of each compound. We have confirmed the slight fermentation activity of the thiazole group. When the thiazole and pyrimidine groups are used together, the length of the induction period is markedly reduced, and in this way the influence of thiazole on the fermentation procedure may be of some consequence. Large errors occur when this method is used for the determination of thiamine in materials having a high sulfite blank. Many foods usually have low blanks but most urines have high blanks. Therefore, the method is a better means of determining the pyrimidine than the thiamine content of urine.

On the basis of hundreds of analyses, the random variation of the method as used for the determination of the pyrimidine group is ( $\sigma_r$ ) = 1.0, the day to day variation ( $\sigma_d$ ) = 0.38, and the over-all variation ( $\sigma_o$ ) = 1.12 (all values in cc  $\text{CO}_2$ ). There is a considerable position difference which may increase the over-all variation by as much as two times. This difference can be eliminated by increasing the speed of shaking. [Sponsorship for this work will be acknowledged in final publication.]

**Synthesis of urea by rat liver homogenates**  
 PHILIP P. COHEN and MIKA HAYANO (by invitation) *Lab of Physiological Chemistry, Univ of Wisconsin*. The synthesis of urea from ornithine, ammonium chloride and carbon dioxide was studied with liver homogenates. Glutamic acid, cytochrome c, adenosine triphosphate (ATP), and magnesium ions are necessary components of the system. Starting with 5 micromols of ornithine, more than 10 micromols of urea are formed by 2.5 mg of tissue N per hour. This demonstrates the catalytic effect of ornithine in urea synthesis by liver homogenates. In the absence of magnesium ions the reaction stops at citrulline. No accumulation of arginine or significant formation of urea occurs, which indicates that magnesium ions may have a more direct role in the conversion of citrulline to arginine than the protection of ATP (required in both steps) from ATPase. In the present system the conversion of ornithine to citrulline by homogenates requires ammonium chloride, carbon dioxide, glutamic acid, cytochrome c, and ATP. The replacement of glutamic acid plus ammonium chloride by glutamine has not given consistent results and its specific role in this reaction is as yet uncertain. Aspartic, lactic, and -keto

glutaric acids are ineffective when substituted for glutamic acid. Neither citrulline nor urea are formed anaerobically.

**Partial purification of a proteolytic enzyme from human serum**  
 PHILIP P. COHEN and L. MAR F. REMBERT (by invitation) *Lab of Physiological Chemistry, Univ of Wisconsin*. The proteolytic enzyme of human serum, plasmin, has been purified approximately 160 fold as determined by a comparison of the proteolytic units per milligram of nitrogen in the original serum and in the final solution. The proteolytic units in the original serum was estimated by salting out the enzyme with ammonium sulfate, redissolving in saline buffer pH 7.4, and determining the activity in the buffer solution. Proteolytic activity was determined by measuring the production of acid soluble tyrosine when the streptokinase activated enzyme was incubated in a 4% casein solution for one hour at 35°C at pH 7.4. Nitrogen in crude preparations was determined by the micro Kjeldahl method, while a modified Nessler procedure was used for samples of higher purification. The original serum was obtained by reconstituting dried human plasma and defibrinating with human thrombin. The purification procedure included alcohol fractionation, adsorption on, and elution from, kaolin, salting out with ammonium sulfate, fractionation with trichloroacetic acid, and a second adsorption on, and elution from kaolin. The solution finally obtained was water-clear, and it contained approximately 13.5 micrograms of nitrogen per milliliter.

**Synthesis of p-aminohippuric acid by liver homogenates**  
 PHILIP P. COHEN and R. W. MCGILVER (by invitation) *Lab of Physiological Chemistry, Univ of Wisconsin*. The synthesis of p-aminohippuric acid (PAH) from p-amino benzoic acid (PAB) and glycine was studied with rat liver homogenates. The synthesis was stimulated by replacement of sodium with potassium, and by 0.00078 M magnesium. It was inhibited 30 per cent by 0.00035 M calcium or fluoride. Phosphate was without effect between 0.01 and 0.06 M. A sharp maximum was obtained at pH 7.50-7.60, necessitating close pH control. 13 per cent of the aerobic synthesis was attained anaerobically. Adenosine triphosphate increased the anaerobic value 50-150 per cent, but no action was obtained aerobically.  $1.2 \times 10^{-6}$  M cytochrome c was required for maximum activity aerobically.

Maximum PAH synthesis was obtained with 0.001 M PAB and 0.015 M glycine. Glycine cannot be replaced by acetate or glyoxylate and ammonia. 0.001 M PAB was completely converted to PAH in 45 minutes by homogenate containing 7 mg of nitrogen.

0.005 M glutamate,  $\alpha$ -ketoglutarate, citrate, succinate, malate, oxalacetate, fumarate, or pyruvate



vate increased the aerobic synthesis 15-60 per cent, the highest values being obtained with malate, citrate, oxalacetate, fumarate, and glutamate. Coenzyme I, thiamin pyrophosphate, and hexose di phosphate were without action. Fumarate showed a maximum increase at 0.0025 M in 45 minute incubations. Without fumarate, the reaction stopped at 35-40 minutes, while with fumarate it continued beyond 65 minutes. A pronounced dilution effect was eliminated by fumarate.

The preparation of fission radioisotopes for radiotoxicological studies. WALDO E. COHEN, *Clinton Labys*,<sup>1</sup> Oak Ridge, Tennessee. The large-scale production of fission for the purpose of creating plutonium poses new problems in health protection because of the unprecedented amounts of new elements which are formed. Many of these are created as pure radioelements and have physical and chemical properties which make them an extreme radiotoxicological hazard. In order to estimate the degree of protection required from these materials, biological experiments—from tracer to toxic levels of activity—were carried out with the purified radioelements.

The chemical requirements placed upon the radioactive preparations used were very stringent. The dependence of radiotoxicity (toxicity due to radiation rather than to chemical nature of the element) upon energies and half lives made the use of the fission radioisotopes themselves mandatory and severely limited the permissible extent of cross contamination of one radioelement with another. Radiochemical separation procedures capable of separating quantitatively, by remote control, free of extraneous solid matter, and in the carrier-free state such similar elements as Ba and Sr, Ce and Y, etc., were required.

The separation of most of the desired fission products in the requisite purity has been accomplished by a process of selective elution of each element from an ion exchanging resin. In certain special cases, coprecipitation or volatilization procedures were useful (e.g., for Sr and I, respectively). The methods and procedures which were developed and which are still in use to produce pure carrier-free fission products from the uranium pile will be presented and discussed.

Kinetics of hemolysis by lysolecithin. H. B. COLLIER, *Dept. of Biochemistry, Univ. of Saskatchewan, Saskatoon*. The photoelectric method of Collier & Wilbur (*J. Lab. Clin. Med.* 29: 1123, 1944) was used to study the kinetics of lysolecithin hemolysis of rabbit erythrocytes in buffered saline. Lysolecithin acts rapidly, its action stopping within 15 minutes. When percentage hemolysis

is plotted against lysin concentration a typical sigmoid curve is obtained, differentiation of this curve gives the resistance distribution of the cell population.

The effect of lowering the temperature is to slow the lytic action, but it proceeds to a greater extent than at higher temperatures. This suggests an adsorption mechanism. Varying the pH of the medium does not markedly affect hemolysis, which shows a maximum at about pH 6.

Copper salts at  $10^{-5}$  M concentration do not affect lysis. Sublytic concentrations of lysolecithin do not alter the cell potassium. Cells spherized by low concentrations of lysolecithin are found to have an increased resistance to hypotonic hemolysis. Acetylphenylhydrazine at M/1000 powerfully accelerates lysolecithin hemolysis, but it has no effect on hypotonic fragility.

Cholesterol added to cell suspensions neutralizes a fixed amount of lysin, irrespective of cell concentration. *In vivo*, cholesterolemia results in a raised plasma antihemolytic value, exactly paralleling the concentration of free cholesterol.

Effects of severe phosphorus deficiency on the metabolism and histology of bone. D. HAROLD COPP, MARIAN J. CRACE and FLORENCE DUFFY (introduced by David M. Greenberg). *Division of Physiology, Univ. of California Medical School, Berkeley*. Severe phosphorus deficiency was produced in rats weaned at 21 days and placed on a diet assaying only 0.008% phosphorus. The diet contained 20% water-washed beef blood fibrin as source of protein. When supplemented with phosphate, it sustained excellent growth in the control animals. Rats fed the deficient diet gained only a few grams in weight, developed severe symptoms within 2 weeks, and died after 3-4 weeks. They exhibited general cachexia and extreme demineralization of the skeleton.

When the deficient rats were injected with radiophosphorus, there was a shift in distribution from bone to soft tissues, and almost complete absence of  $P^*$  from the urine. When radiostrontium was injected, the retention in bone was greatly reduced in the phosphate deficient animals, the difference being reflected in an increased excretion of  $Sr^*$  in the urine. The distribution of both  $P^*$  and  $Sr^*$  resembled that in rachitic rats.

However, in contrast to the overgrowth of cartilage associated with rickets, histological sections of bones from the phosphate deficient rats revealed a narrow epiphyseal zone with numerous osteoclasts below it, and only a thin shell bone salt remaining in the shaft.

These findings indicate the inhibition of growth of soft tissues and extreme demineralization of bone associated with severe phosphorous deficiency.

Gluc- and fructokinase in mammalian tis-

<sup>1</sup> Operated by Monsanto Chemical Company for the U. S. Atomic Energy Commission.

sues GERTY T CORI and MILTON W SLEIN (by invitation) *Dept of Biochemistry, Washington Univ School of Medicine, St Louis* Crystalline yeast hexokinase catalyzes the transfer of phosphate from adenosine triphosphate (ATP) to glucose, fructose, and mannose. Evidence has been obtained that in mammalian tissues there are separate enzymes for the phosphorylation of glucose and fructose. Ground rabbit or rat muscle was extracted with 0.03 N KOH. Extraction and subsequent fractionations were carried out at 0°. The extract was brought to pH 6 with dilute HCl and a precipitate removed by centrifugation. The precipitate which formed in the supernatant fluid with 30% acetone was centrifuged, dissolved in 0.03 M veronal pH 7.6 and dialyzed for 1-2 hours against the same buffer. This protein fraction catalyzed the reaction between glucose and ATP, while fructose was not phosphorylated.  $Mg^{++}$  ions were necessary for enzyme activity, the reaction product was found to be fructose-1,6-diphosphate. Since the enzyme fraction under the conditions of the experiment did not convert glucose-1- to glucose-6-phosphate, the primary product of phosphorylation may be assumed to be glucose-6-phosphate. When rabbit muscle extract, obtained as above, was fractionated with ammonium sulfate, the protein which precipitated between 41 and 50% saturation (pH 7.6) was found to catalyze the phosphorylation of fructose, but not of glucose.  $Mg^{++}$  ions were necessary for activity and the reaction product was again shown to be fructose-1,6-diphosphate. The same enzyme fraction converted added fructose-1- as well as fructose-6-monophosphate to fructose-1, 6-diphosphate. Further fractionation with ammonium sulfate resulted in an enzyme preparation which acted on the two fructose-monophosphates, but not on free fructose. Evidence for the presence of separate gluco- and fructokinases has also been obtained for liver tissue.

**Species difference in nitrogen retention, the effect of adding methionine to an enzymic casein hydrolysate** WARREN M COX, JR., ARTHUR J MUELLER (by invitation), ROBERT ELMAN (by invitation), ANTHONY A ALBANESE, and L EMMETT HOLT, JR. *Dept of Nutritional Research, Mead Johnson and Company, the Dept of Surgery, Washington Univ School of Medicine and Barnes Hospital, St Louis, and the Dept of Pediatrics, New York Univ and Bellevue Hospital, New York*. The addition of cystine or methionine to low intake levels of a casein hydrolysate (Amigen) has been shown to give an increase in the rate of growth of rats comparable to that attained by the feeding of identical levels of lactalbumin as the sole source of protein. When administered orally, subcutaneously, or intravenously to dogs, the supplementation of the casein hydrolysate with

methionine resulted in improved nitrogen retention, whereas the addition singly of the other nine essential amino acids had no such effect.

Similar experiments in man gave entirely different results. In four different investigations conducted at three separate institutions the addition of methionine or cystine to the casein hydrolysate did not increase nitrogen retention. This was true in surgical patients to whom the material was given intravenously, in infants fed a luxury level of nitrogen, in six well adults fed a maintenance level of nitrogen, and in four well adults who were protein depleted for 21 days and subsequently given minimal amounts of the casein hydrolysate with and without added methionine.

The findings are interpreted to mean that there is a species difference in the requirement for methionine because supplementation of a casein hydrolysate with this amino acid improved its nutritional value for the rat and dog, but did not do so for man. The implications of the findings are discussed. Experiments with human subjects are now in progress to determine the relative nutritional value of lactalbumin and casein for man.

**Studies on the formation of isotopic acetoacetate in homogenized liver** DANA I CRANDALL (by invitation), SAMUEL GURIN and D WRIGHT WILSON. *Dept of Physiological Chemistry, School of Medicine, Univ of Pennsylvania, Philadelphia*. The conversion of isotopically labelled pyruvate to acetoacetate was studied in a washed suspension of rat liver described by Lehninger.<sup>1</sup> It was found that pyruvate labeled in the  $\alpha$  and  $\beta$  positions with  $C^{13}$  gave rise to acetoacetate with isotope equally distributed among all four carbons, thus proving that the acetoacetate arises exclusively from the  $\alpha$  and  $\beta$  carbons of pyruvate.

Although acetate does not give rise to acetoacetate in this preparation,<sup>2</sup> it was found that a small but significant conversion of acetate to acetoacetate occurred in the presence of pyruvate.

Acetate tagged with  $C^{13}$  in the carboxyl position and non isotopic pyruvate were equilibrated with the rat liver suspension and the resulting acetoacetate was found to contain isotope equally distributed between the carboxyl and carbonyl carbons. These results suggest that in the presence of pyruvate the acetate either condensed with itself or condensed with 2 carbon fragments derived from pyruvate to form an equimolar mixture of carboxyl and carbonyl labeled acetoacetate.

**Precision of microbiological assays for riboflavin, niacin and pantothenic acid** W A CRANDALL and MURIEL M BURR (introduced by L I Pugsley). *Food and Drugs Divisions, Dept National Health and Welfare, Ottawa, Canada*

<sup>1</sup> Lehninger, A. L. J. B. C. 161: 437 (1946)

<sup>2</sup> Lehninger, A. L. J. B. C. 164: 291 (1946)

Data obtained from microbiological assays for each of the three named factors will be presented, and the precision of each method estimated by the methods of Wood and Finney (*Quart J Pharm Pharmacol* 29 112, 1946) and Bliss (*Ann Math Sc* 17 232, 1946). Comparisons of the precision of 3-point, 5 point, 7 point and 9 point assays will be given. Validity of the calculated precision will be shown by data from repeat assays on the same sample.

**The effect of tocopherol feeding on the tocopherol and peroxide content of turkey tissues** JOY E CRIDDLE (by invitation) and AGNES FAY MORGAN *Laby of Home Economics, Univ of California, Berkeley* Mixed tocopherols, 4.2 or 0.4 gm per bird in 35 days before slaughter, were fed to 12 turkeys in one series and in another series, 32.9 gm in 21 days, 11.3 in seven days, 3.4 or 8.7 in two and one half days, to 16 turkeys. All received the standard basal diet, but for one group this was made vitamin E free by ferric chloride treatment. The tissues of one bird in each group were examined for rancidity, peroxide and tocopherol content immediately after slaughter, and after 3, 5 or 6, or 9 months frozen storage. Both a modification of the Emmerie and Engel chemical method and the rat bioassay were used for the tocopherol analyses. The tocopherol deposits, which were widely distributed in the tissues, but most concentrated in the liver and heart, represented only a small fraction of the extra vitamin fed. The liver concentration was increased 6 times by the largest dosage, while that of the other tissues was usually only doubled.

A decrease in peroxide development during storage in the fat of the treated birds was noted parallel with the increase in the tocopherol content of the tissues. The meat of the control birds on the unsupplemented ration developed unpleasant flavors during prolonged storage. This was not true of the treated birds. The chemical and bioassay methods for tocopherols yielded comparable values thus indicating that the substances determined were tocopherols and that their presence retarded the march of rancidity.

**Nitrogen content of three foreign proteins (toxins)** H. R. CROOKSHANK (by invitation) and EMMETT B. CARMICHAEL *Biochemistry Dept Medical College of Alabama, Birmingham, Alabama* Tetanus toxin, dried rattlesnake venom, and ricin were analyzed for total nitrogen content by a modified micro Kjeldahl method and for amino nitrogen content by the Van Slyke manometric method.

Tetanus toxin contained 15.71 per cent total nitrogen and 1.55 per cent amino nitrogen, rattlesnake venom 14.90 per cent total nitrogen and 1.98 per cent amino nitrogen, and, ricin 16.62 per

cent total nitrogen and 2.63 per cent amino nitrogen.

**Utilization of amino acids by the chicken embryo** FRANK A. CSONKA and M. W. OLSEN (by invitation) *Bureau of Human Nutrition and Home Economics and the Bureau of Animal Industry, Agricultural Research Administration, United States Dept of Agriculture, Washington* In previous experiments it was shown that the amino acid content of a chicken egg can be changed by dietary means. One may enrich the egg amino acid content in a more direct way by introducing the amino acid into the egg, using sterile precautions. By introducing 50 mg of dl-methionine into each of several eggs and incubating the eggs, we succeeded in following up the utilization of methionine by the embryo. The embryo was removed and the remaining portion of the egg was quantitatively transferred into a small cellophane bag, tied and dialyzed for 3 to 4 days against distilled water (changed twice) at 5°C temperature. The methionine in the combined dialysates was determined colorimetrically.<sup>1</sup> The quantity of added synthetic methionine diminished progressively with the aging of the chick embryo. After 5 days of incubation, 33.2 mg methionine, after 12 days, 21.6 mg, and after 17 days, no methionine was detectable in the egg dialysate. Obviously, both optical isomers of methionine are available for the chick embryo. No free cystine or methionine was present in the dialysate of egg contents obtained from a freshly laid egg or from incubated ones (after the embryo was removed) serving as controls. This method will be applied to other racemic amino acids to establish their availability to the embryo and to growth in general.

**A method for purification of subtilin** K. P. DIMICK (by invitation), G. ALDERTON (by invitation), H. D. LIGHTBODY and H. L. FEVOLD (by invitation) *Western Regional Research Laby,<sup>2</sup> Albany, Calif* Subtilin is extracted from surface or submerged cultures of *Bacillus subtilis*, adjusted to pH 2.5 with HCl, with  $\frac{1}{2}$  to 1 volume of N butyl alcohol. The two phases are separated with a Sharples centrifuge and  $\frac{1}{2}$  volume of petroleum ether added to the wet butyl alcohol extract. The butyl alcohol-petroleum ether mixture is extracted three times with 1/10 volumes of 1% acetic acid. Sodium chloride is added to the combined aqueous extracts to 6% concentration. A precipitate separates which collects on the surface and is skimmed off. The precipitate is washed with petroleum ether and the excess salt solution removed by filtration. The filter cake is dried by lyophiliza-

<sup>1</sup> Csonka, F. A. and C. A. Denton, *J. Biol. Chem.* 163 329 (1946).

<sup>2</sup> Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

tion and extracted with 95% alcohol (five or six times with 20 ml per gram) and subsequently in a similar manner with 85% ethyl alcohol containing 1% NaCl and 1% acetic acid. The extracts are discarded. The alcohol insoluble residue is dissolved to a concentration of 1% in distilled water. The pH is adjusted to 4.5 with dilute NaOH and 0.4% NaCl added. The precipitate is removed by centrifugation, redissolved and reprecipitated as before. This is repeated three or four times. The active extracts are deionized by ion-exchange resins and dried by lyophilization, or the active material may be concentrated by precipitation with 10% NaCl and subsequently dissolved, deionized and dried.

**New characteristic color reactions of carbohydrates with SH compounds in  $H_2SO_4$ .** ZACHARIAS DISCHE, *Dept of Biochemistry, Columbia Univ.* All carbohydrates give with  $H_2SO_4$  above 70° decomposition products which react with SH compounds, with formation of colored products. The character of the reaction depends on the concentration of  $H_2SO_4$ , time of heating, the nature of the sugar and of the SH compound. The following procedure has proved appropriate for tentative identification and determination of sugars in polysaccharides. To 1 cc of the sugar solution 4.5 cc of a mixture of 1 vol  $H_2O$  and 6 vol  $H_2SO_4$  are added with ice cooling. The mixture is brought to 22° and then kept 3 minutes in boiling water. After cooling 0.1 cc of 2.5% solution of cysteine is added. The mixture is allowed to stand at room temperature 24 hours. The following colors are given by various sugars: Methylpentoses—green-yellow, Pentoses—pink, Mannose—yellow, glucose—green, galactose—blue, fructose—brown, sorbose—blue. Ratio density at 6000 Å density 5400 Å is much higher for galactose than glucose and mannose and galactose can be easily distinguished from mixtures of equal parts of glucose and mannose, which is difficult with the procedure of Gurin and Hood based on the carbazole reaction. This latter procedure combined with the new one makes possible the determination of all three sugars in the same solution even in presence of 0.5% protein. Methylpentoses are determined in presence of large excess of hexoses by heating the reaction mixture 10 minutes instead of 3 and measuring the decrease of the absorption in blue due exclusively to hexoses.

**Specific color reactions of glucuronic and galacturonic acids.** ZACHARIAS DISCHE, *Dept of Biochemistry, Columbia Univ.* Two color reactions usable for tentative identification of hexuronic acids in polyuronides were found. I. *Mannose-thioglycolic acid reaction of glucuronic acid.* To 0.8 cc of a 0.005–0.040% solution of glucuronic acid 0.2 cc of 0.2% mannose solution are added. 4.5 cc of a mixture of  $H_2O + 6 H_2SO_4$  are added

with ice cooling, samples brought to room temperature and then 3 minutes kept in boiling water. After cooling 0.1% of a 2.5% of thioglycolic acid solution are added. After 24 hours a pink color appears with characteristic sharp absorption maximum at 5400 Å. The blank containing mannose and thioglycolic acid is green-yellow. Hyaluronic, chondroitinsulphuric acids and pneumococcus polysaccharide T III show the reaction corresponding to their content in glucuronic acid, not galacturonic, pectic, alginic acids and pneumococcus polysaccharide T I, showing instead a brown color with flat minimum at 5100 Å. II. *Cysteine reaction of galacturonic acid.* 1 cc of 0.08–0.1% solution of galacturonic acid is mixed with 4 cc of  $H_2SO_4$  in water bath of 22°. After cooling 0.1 cc of 2.5% solution of cysteine is added. After 24 hours a green-blue color appears. The absorption curve shows a steep rise between 5400 and 5800 Å and flat maximum at 6000 Å. Pectic acid and pneumococcus polysaccharide T I show the reaction, glucuronic acid, polyglucuronides, alginic acid do not.

**Observations on the composition of heparin and the nature of its hexuronic constituents.** ZACHARIAS DISCHE and KARL MEYER, *Depts of Biochemistry and Ophthalmology, Columbia Univ.* Two barium salts of heparin were prepared and compared with crystalline barium salt of Charles and Scott analyzed previously. I. Water insoluble salt, II. crystalline salt. Analysis of anhydrous salt: I. N 1.81%, S 11.5%, C 19.2%. Hexuronic acids, 21.5%, Acetyl 0.2%, N S C = 1.08.3.13.3. II. N 1.89%, S 11.6%, C 19.7%. Hexuronic acids 22.2%, Acetyl 0.7%, N S C = 1.12.3.13.7.

The Mannose-thioglycolic acid reaction for glucuronic acid was negative for I and slightly positive in II, corresponding to about 20% of the hexuronic acid of the preparation in form of glucuronic acid. The cysteine reaction for galacturonic acid was positive in both preparations. The shape of the absorption curves of I was in both reactions almost identical with that of galacturonic acid. With the carbazole reaction for hexuronic acids heparin shows a behavior different from that of all other known mucopolysaccharides, except that from amyloid tissue. Data on oxidation of heparin with bromine in acid solution are presented and the implication of all these data for the structure of heparin and the nature of its hexuronic constituent are discussed.

**The determination of antihyaluronidase in human blood.** ALBERT DORFMAN, MELVIN L. OTT, and ELIZABETH J. REINIERS (introduced by Ralph I. Dorfman), *Army Medical Dept Research and Graduate School, Army Medical Center, Washington 12, D C.* Several authors have reported the existence of a substance in human blood which inhibits or destroys hyaluronidase prepared from

beef testes Haas has recently studied this substance in detail and has concluded from kinetic studies that it is an enzyme

Using a viscosity method for the estimation of hyaluronidase similar to that used by Haas, we have found that the reaction between hyaluronidase and antihyaluronidase is virtually complete in three minutes despite the presence of unreacted hyaluronidase These data suggest that this reaction is not enzymatic in nature Identical results were obtained by a turbidity method based on the mucin clot prevention test

Antihyaluronidase (to bull hyaluronidase) was found in all human bloods tested irrespective of previous exposure to bull hyaluronidase Wide variations in different individuals were found Data will be presented showing the relationship of antihyaluronidase to age and sex

The bioassay of various hormones using a simplified experimental design RALPH I DORFMAN *From the Depts of Biochemistry and Medicine, Western Reserve Univ School of Medicine and Lakeside Hospital, Cleveland 6, Ohio* The statistical method suggested by Bliss (J Amer Stat Assoc 39, 479 (1944)) for the determination of the relative potency of biological materials and its standard error has been applied to the assay of the androgens such as testosterone propionate using the chick's comb, the assay of chorionic gonadotrophins using the uterine response of the immature female rat, the assay of the adrenal cortical hormones by the glycogen deposition technique in adrenalectomized mice and rats, and the assay of thyrotrophic hormone using the uptake of radioiodine by the thyroids of the chick Typical calculations will be illustrated and the sensitivity and reproducibility of the various bioassay methods within the specific conditions employed will be discussed

Liver regeneration and cytochrome c metabolism Influence of diet and anoxia DAVID L DRABKIN *Depts of Physiological Chemistry, School of Medicine and Graduate School of Medicine, Univ of Pennsylvania, Philadelphia* In a continuation of studies on the metabolism of cytochrome c in partially hepatectomized rats, cytochrome c has been shown to be an important component in the regenerative process

Excision of two-thirds of the liver resulted in more rapid regeneration and appreciably greater new cytochrome c than after removal of one-third On a high (32 per cent) protein diet, the amount of liver restored was nearly as great and the amount of new cytochrome c was as great (or greater) at 4 days of regeneration as after 14 days Thus, based on analyses 4, 6, and 14 days after excision of two thirds of the organ, the respective rates of appearance of new cytochrome c in liver were 16,

11, and 5 per cent per day in rats on the high protein diet

On a non protein diet regeneration (at 14 days) was less than on high protein, but the percentage of new cytochrome c was similar on the two diets Indeed, per gm dry weight of tissue cytochrome c was significantly higher in the partially restored livers of the protein depleted animals Transfer of such animals to the high protein diet resulted in remarkable liver regeneration of 151 per cent, with 81 per cent of new cytochrome c

Incorporation of injected cytochrome c in regenerating liver was not demonstrated Living at simulated moderate high altitude of 15,500 feet was without effect on regeneration and cytochrome c

The influence of acetylsalicylic acid ingestion on the electrophoretic patterns of plasma ROBERT L DRYER (by invitation), W D PAUL (by invitation), and JOSEPH I ROUTH *Depts of Biochemistry and Internal Medicine, College of Medicine, State Univ of Iowa, Iowa City* Normal healthy subjects ingested 60 grains of acetylsalicylic acid per day for one week Plasma samples were obtained at the beginning and end of the week After dilution with 3 volumes of buffer (0.1 N sodium diethylbarbiturate, pH 8.6, and 0.1 ionic strength) the plasma was dialyzed at 5°C for 3 days with daily change of buffer Electrophoresis was conducted at 0.8°C in the Longworth modification of the Tiselius apparatus

The concentration of the protein components in patterns of plasma obtained before acetylsalicylic acid ingestion showed good agreement with published values for plasma from normal adults Although there were no marked changes apparent in the patterns after ingestion of acetylsalicylic acid, planimetric analysis revealed quantitative differences in the components On a percentile basis of total protein the albumin and  $\gamma$  globulin showed a slight decrease, the  $\alpha$  globulin a more marked decrease, whereas both fibrinogen and  $\beta$  globulin were increased

The effects of pH on the respiration of brain slices and suspensions K A C ELLIOTT and MARIO K BIRMINGHAM (by invitation) *Montreal Neurological Inst, McGill Univ* With slices of various guinea pig tissues, Canzanelli *et al*<sup>1</sup> found maximum rates of respiration in medium of surprisingly high pH With brain slices the optimum was at pH 9-9.5 With rat brain slices we have found maximum respiration rates between pH 7.5 and 9.5

With isotonic suspensions of rat brain a broad optimum pH for respiration was found around 7.4 Above pH 8 there was definite loss of activity, at

<sup>1</sup> Canzanelli A, Greenblatt M, Rogers, G A., and Rapport D *Am J Physiol* 127: 290 (1939)

pH 9.5 the rate was decreased by about 75 per cent

The high apparent optimum found with slices suggested that the pH of the medium does not represent the pH of the slice itself. The actual pH of rat brain slices in well aerated Ringer-phosphate, Ringer-bicarbonate, or serum, was measured by means of a micro glass electrode gently lowered onto the tissue which was supported on cheese cloth stretched over a frame. The pH of the slice was found to be definitely lower than that of the medium at all pH values above 6, and above it at pH values below 6.

pH of medium	9.0	7.5	6.0	4.5
pH of slice	7.0±	6.5±	5.9	5.2

While a slice is respiring, the concentration of lactic acid is higher within the slice than in the medium, 7 to 8.5 vs. 1.4 to 4.0 mM, but the difference is probably not sufficient to affect the pH appreciably. More probably the difference in pH between the slice and medium is due to slowness of diffusion of respiratory  $\text{CO}_2$  out of the slice.

**Chemical studies on the antibiotic, fumigacin.** WILLIAM H. ELLIOTT (by invitation), PHILIP A. KATZMAN, SIDNEY A. THAYER and EDWARD A. DOISY *Laby of Biological Chemistry, Saint Louis Univ. School of Medicine, Saint Louis, Missouri.* The antibiotic, Fumigacin, has been isolated from culture filtrates of *Aspergillus fumigatus* which was grown on a modified Czapek-Dox medium containing brown sugar in place of glucose and a supplement of black strap molasses. After forty days of incubation at 23–25°, crude material was precipitated from the culture fluids by acidification. The pure product was prepared by decolorizing an acetone solution with norite and recrystallizing from methanol and ethanol. Fumigacin crystallizes in long, fine, colorless needles, m.p. 210.5–211° (heated at the rate of one degree per minute),  $[\alpha]_D^{25} = -130 \pm 1^\circ$ . These properties agree with the values of Menzel, et al.,<sup>2</sup> Chan and associates<sup>3</sup> and Birkinshaw, et al.<sup>4</sup>

Fumigacin takes up three moles of hydrogen over reduced  $\text{PtO}_2$  in ethanol to give hexahydrofumigacin. This derivative crystallizes from aqueous alcohol as long silky, colorless needles, m.p. 188.5–189.5°,  $[\alpha]_D^{25} = -87 \pm 1^\circ$ . It forms an acetate, m.p. 147.5–148°, indicating that the carbonyl group of fumigacin has been reduced to a hydroxyl group.

By hydrogenation over reduced  $\text{PtO}_2$  in glacial

acetic acid, fumigacin takes up four moles of hydrogen to give octahydrofumigacin. This material is obtained from aqueous alcohol as colorless crystals, m.p. 223.5–224.5°,  $[\alpha]_D^{25} = -81 \pm 1^\circ$ . Quantitative acetylation showed the presence of one hydroxyl group.

Fumigacin shows a maximum in the ultraviolet,  $E_{1\%}^{1\text{cm}} = 300$  (230 m $\mu$ ), hexahydrofumigacin exhibits only end absorption beyond 220 m $\mu$ , and octahydrofumigacin shows no appreciable absorption.

Fumigacin reacts with three moles of alkali, liberating two moles of volatile acid, subsequently identified as acetic acid. Similar results were obtained with the hexahydro derivative (Work done under contract, recommended by the CMR, between the OSRD and St. Louis University).

**Nutritional Studies on the formation of subtilin by *Bacillus subtilis* in surface cultures.** R. E. FEENEY (by invitation), E. M. HUMPHREYS (by invitation), H. D. LIGHTBODY and J. A. GARIBALDI (by invitation) *Western Regional Research Laby,<sup>1</sup> Albany, Calif. Synthetic Medium.* Moderate growth and subtilin formation have been obtained on synthetic media. Yields of 600–800 mg/l of antibiotic have been obtained after 60–72 hours of incubation in shallow layer cultures on the following medium: sucrose, 100 g; asparagin, 20 g; glutamic acid, 20 g; citric acid, 0.5 g;  $\text{Na}_2\text{SO}_4$ , 40 g;  $(\text{NH}_4)_2\text{HPO}_4$ , 80 g; NaCl, 0.30 g; inorganic salts, and distilled water to give 1 L of medium. The essential mineral elements were (expressed in parts per million): Zn, 20; Fe, 40; Mn, 50; Mg, 50; and K, 100. Ca exerted a markedly deleterious effect.

**Zinc, an Essential Element.** A 30 fold increase in antibiotic formation was obtained by the addition of Zn to a Zn-free medium. Removal of Zn was accomplished by extractions with carbon tetrachloride solutions of diphenylthiocarbazone. Slight growth and antibiotic yields of <20 mg/l were obtained in this medium. A linear response in antibiotic formation was obtained with Zn additions from 0.03 to 1.0 ppm. One to 100 ppm Zn gave good growth and antibiotic yields of over 600 mg/l. Preliminary results indicate this requirement for Zn to be specific. Similar alterations of bacterial metabolisms by Zn appear to be heretofore unobserved.

**Some factors influencing the structure and rate of formation of fibrin clots.** JOHN D. FERRY, JOHN T. EDSALL, PETER R. MORRISON (by invitation), VICTOR KIMEL (by invitation), and WALTER F. LEVER (by invitation) *Dept. of Physical Chemistry, Harvard Medical School.* The rate of fibrin

<sup>1</sup> All melting points uncorrected.

Menzel, A. E. O. Wintersteiner and J. C. Hoogerheide *J. Biol. Chem.* 152: 419, 1944.

Chan, E. H. W., Florey, M. A., Jennings, and T. I. Williams *Brit. J. Exp. Path.* 24: 108, 1943.

<sup>4</sup> Birkinshaw, J. H. A., Bracken, and H. Rustrick *Biochem. J.* 39: 70, 1945.

<sup>1</sup> Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

formation, in solutions of human fibrinogen and thrombin, has been studied as a function of fibrinogen and thrombin concentrations, pH, ionic strength ( $I/2$ ) and temperature. Fibrin was determined by weighing the washed and dried clots. Solutions were free of prothrombin, and no fibrinolytic substance was present in significant amount. The initial rate of clotting was approximately linear in the thrombin concentration, when the latter was varied between 0.02 and 0.20 unit/ml. It was also first order with respect to fibrinogen concentration, but no simple analysis of the later stages of the reaction could be made.

The structure of the clot is profoundly affected by conditions.<sup>1</sup> "Coarse type," opaque, readily synergizing clots are produced near pH 6.3 at low  $I/2$ , "fine type," translucent, friable clots at pH 7 or above, and also at high  $I/2$ . Certain ions—notably iodide, thiocyanate, acetyltryptophanate—and some non ionic substances like urea, alter the properties of the clots to the "fine type," even at pH 6.3,  $I/2$  0.15, where "coarse clots" are ordinarily produced. Most of these reagents, at high concentrations, are well known protein denaturants, but their effect on fibrin clots is profound even at very low concentrations. All these reagents also greatly diminish the opacity of the clot and the rate of clotting, independent tests showed that this was not due to inactivation of thrombin. Guanidine hydrochloride at 0.05–0.08 M also greatly retards clotting, but does not modify clot structure in the same way.

Relation of reducing intensity to streptomycin susceptibility of bacteria. ELLA H. FISHBERG, ERICH SELIGMANN (by invitation), and MICHAEL WASSERMANN (by invitation). *Labys of Beth Israel Hospital, New York City*. Reductants such as glucose and ascorbic acid diminish the activity of streptomycin *in vitro* (Waksman). 2–6 dichlorophenolindophenol is progressively reduced by a growing bacterial culture and the rate of drop in potential  $dE_h/dT$  through the indicator zone becomes a measure of the reducing intensity of the organism. This was followed potentiometrically in bacterial cultures of known streptomycin susceptibility.

The U-shaped electrode vessel containing 16 cc of plain broth, 9 cc of 0.004 M solution of 2–6 dichlorophenolindophenol in phosphate buffer (pH = 7.2) was seeded with 6 drops of a 24-hour broth culture. The  $E_h$  of the culture was determined at frequent intervals. Temp 37°C.

The slopes of the time potential curves of organisms of varying streptomycin susceptibility fell into 3 categories. One group maintained a potential well within the range of the indicator

over 12 hours, the next passed more rapidly through this zone and the last raced through. Streptomycin was extremely toxic to the first group, (1 unit active), less toxic to the second, (4–8 units) and exerted little influence on the third (more than 24 units). A *Staphylococcus aureus* susceptible to 1 unit in plain broth showed a curve corresponding to an organism of higher resistance when measured growing in glucose broth.

Streptomycin may lose the greater part of its toxicity for a bacterial culture when grown under conditions that preclude the attainment of a sufficiently high  $E_h$  either through externally added reductants such as glucose etc., or by the endogenous reducing intensity developed within the organism itself.

Excretion of benzoquinone acetic acid in acute rheumatic fever. ELLA H. FISHBERG and VIRGINIA RECHNITZER (by invitation). *From the Labys of Beth Israel Hospital, New York City*. If an adequate quantity of vitamin C is unavoidable ingested tyrosine does not proceed through the customary channels of catabolism but is excreted as partial metabolites of aromatic structure. We have obtained from the urine of 14 children suffering from acute rheumatic fever a substance which may be assumed to be benzoquinone acetic acid, the oxidized phase of the redox system homogentisic-benzoquinone acetic acid on the basis of the following characteristics.

It liberates iodine from acidified KI which turns deep blue on the addition of starch. It is precipitated by 2–4 dinitrophenylhydrazine yielding a compound of M.P. 162°. On addition to blood there is rapid formation of methemoglobin, reduction in the oxygen combining power of the blood, and the typical bands of methemoglobin become visible spectroscopically. Its  $E_h$  as determined by potentiometric titration with leuco indigo carmine is +4.3 volts at pH 4. Its ultraviolet absorption spectrum is characterized by a maximum at 285 Å and a flat minimum between 265 and 200 Å.

For clinical purposes it may be quantitatively determined by adding 10 cc of 10% KI and 10 cc of 2N H<sub>2</sub>SO<sub>4</sub> to 20 cc of urine and titrating with N/100 thiosulfate using a starch indicator. The cc thiosulfate  $\times 2.7$  % mg quinone in 100 cc of urine. During the periods of quinone excretion the output of ascorbic acid as determined by 2–6 dichlorophenolindophenol titration is extremely low.

$\beta$ -Glucuronidase in the metabolic conjugation of estrogenic hormones. WILLIAM H. FISHMAN (introduced by E. A. Evans, Jr.) *Depts of Surgery and Biochemistry, Univ of Chicago, Chicago, Illinois*. Glucuronide formation has generally been considered a process of "detoxication." However, this term with its pharmacological connotation, cannot be applied properly to the formation of

<sup>1</sup> J. D. LARRY and P. R. MORRISON. J. Am. Chem. Soc. 69 (in press) (1947).



estriol and pregnanediol glucuronides in pregnancy. It is proposed that glucuronide formation in all cases be regarded as one of the processes of "metabolic conjugation," the purpose of which should be settled in each instance on the basis of the available evidence.

$\beta$ -Glucuronidase appears to catalyze the synthesis of glucuronides as evidenced by the elevation of glucuronidase activity in liver, kidney, and spleen following menthol feeding. There was no increase in uterine  $\beta$ -glucuronidase activity. However, small amounts of estrogen produced a prompt increase in activity of the uterine enzyme. This specificity in the site of action of these agents suggested that glucuronidase participated in the tissue transport or metabolism of the estrogens. This hypothesis was tested by treating ovariectomized mice with various estrogens, natural and artificial. An increase in enzymic activity was found in the uterus and not in several other tissues. The effective dose of estrogen was very small, well within physiological limits, so that the response obtained appears to be a normal tissue reaction rather than an attempt upon the part of the organism to deal with a foreign toxic agent by conjugation and elimination. Accordingly, the elevation in uterine glucuronidase may be considered as a physiological response to estrogen in which glucuronide formation is the initial step in the utilization of the hormone by the tissue.

Phospholipids of lymph following feeding of fat to dogs. E. V. FLOCK, J. C. CAIN (by invitation), J. H. GRINDLAY and J. L. BOLLMAN. *Division of Experimental Medicine, The Mayo Foundation, Rochester, Minnesota*. Lymph was collected from the thoracic duct through flexible plastic tubing one or more days after the dogs had recovered from the surgical anesthetic. In the fifteen dogs studied the concentration of phospholipids of the lymph during fasting was less than that of the plasma. This was not materially increased after feeding a fat-free meal but following phospholipid-free meals containing neutral fat increases of phospholipid concentration in the lymph were found. The maximum increase over the control fasting values was usually attained about six hours after feeding and was from two to five times the fasting value. Large increases in the neutral fat of the lymph were found at the same time and small increases in the cholesterol content of the lymph were also noted. When the meal contained free fatty acid but no neutral fat a marked increase in the phospholipid and neutral fat content of the lymph also occurred.

In eight dogs radioactive phosphorus, as sodium phosphate, was injected intravenously when the meal was given. The specific activity of the phospholipid of the lymph from these dogs was often higher than that of the plasma. Not all of the

phospholipid of the lymph could have been derived from the plasma. Additional experiments with radioactive phosphorus and lymph collected directly from the liver lymphatics and from the intestinal lymphatics indicated that new phospholipid was being added to the lymph from the intestine and also some from the liver. A fat meal produced a much greater increase of phospholipid from the intestine than from the liver.

Isolation of a soy bean phosphatide containing carbohydrate, inositol and glycerol as constituents. JORDI FOLCH. *McLean Hospital, Waverley, Mass. and Harvard Medical School*. This phosphatide is obtained by the following procedure. Oil-free soy bean phosphatides are purified by dialysis and lyophilized. They are dissolved in 6 parts of chloroform by weight and the solution treated with 9 parts of ethanol by volume. A viscous underlayer separates on standing, which is collected and dried. The material is dissolved in 15 parts of chloroform by weight and the solution treated with an equal volume of methanol. A viscous underlayer separates and is collected and dried. The chloroform-methanol treatment is repeated twice after which a material of constant composition is obtained. The yield is 10 per cent of starting phosphatides.

The material is an acidic phosphatide. It is obtained as a mixed salt of calcium, magnesium and potassium and contains one equivalent of base per atom of P. Its elementary composition is as follows (per cent): C 54.0, H 8.3, N (all as  $\text{NH}_2\text{-N}$ ) 0.72 and P 3.15. Among its products of hydrolysis have been isolated inositol and fatty acids and on analysis it is shown to contain carbohydrate, glycerol and phosphoric acids. These constituents appear to be present in the following molar ratios: Amine I,  $\text{H}_2\text{PO}_4$  2, inositol 2, carbohydrate (as galactose) 2, glycerol 2, and fatty acids, 3.

A study of the possible lipotropic action of a dried stomach preparation. J. C. FORBES and OLGA PETTERSON. *Medical College of Virginia, Richmond, Virginia*. Gillman and Gillman<sup>1</sup> showed that the administration of a dried stomach preparation, Ventriculin, to patients with infantile pellagra brought about rapid clinical improvement and a rapid return of the characteristic fatty livers to a normal fat content. In view of these findings it was decided to determine whether this preparation exerted a lipotropic effect in animals on a choline-free, low-protein, high-fat diet. The diets used contained 40 grams fat (Crisco), 5 or 10 grams vitamin-free casein, 1 gram Cellu Flour B, 3 grams salt mixture, and sucrose to make 100 grams, plus adequate amounts of vitamins A, D, thiamine, riboflavin, pantothenic acid, niacin and pyridoxine. The dried stomach preparation was

<sup>1</sup>Gillman, T. and Gillman, J., J. A. M. A. 129: 12 (1943)

added to the diet at a level of either 0.2, 0.5 or 2 grams per 100 grams of diet. It was found that the preparation possessed no definite lipotropic action against this form of nutritional fatty livers.

**Inhibition of bacterial growth by amino acid enantiomorphs and their derivatives.** SIDNEY W. FOX, MARGUERITE FLING (by invitation), YUTAKA KOBAYASHI (by invitation), and FREDERICK N. MINARD (by invitation) *Chemical Lab., Iowa State College*. The inhibition of bacterial growth by *D* amino acids and derivatives has been of interest because of its relationship to microbiological assay, to protease activity, to retardation of growth in animals, and to the antibiotics, gramicidin and penicillin.

The *D* isomers of leucine and valine have been shown to retard the growth of such bacteria as *Lactobacillus arabinosus* and *Escherichia coli*. Formyl derivatives have inhibited the growth of *Staphylococcus aureus*. The use of a turbidimetric technique has permitted more precise evaluation of some of these inhibitions. In particular, the type of antipodal specificity which had earlier been found for *L. arabinosus* has now been observed to apply to *E. coli*. When the effects of the enantiomorphs of alanine, valine, and leucine were compared, a close correspondence to the antipodal specificity of the amino acid residues in Bergmann's substrates for proteolytic enzymes was found. *D*-Alanine showed less inhibition of *E. coli*, on a molar basis, than did *D*-valine or *D*-leucine.

In the search for more strongly antibacterial *D* amino acid derivatives, prolyl and phthalyl derivatives of *D*- and *L* isomers of valine and leucine have been prepared. The phthalyl derivatives were synthesized by condensing each of the amino acids with phthalic anhydride. The prolyl derivatives were prepared by the following reaction sequence: cyclopentanone  $\rightarrow$   $\sigma$ -hydroxyvaleric acid  $\rightarrow$   $\sigma$ -bromovaleric acid  $\rightarrow$   $\alpha,\sigma$ -dibromovaleric acid  $\rightarrow$   $\alpha,\sigma$ -dibromovaleryl chloride  $\rightarrow$   $\alpha,\sigma$ -dibromovaleryl amino acid  $\rightarrow$  prolyl amino acid. Some physical properties of these peptides have been recorded.

**Possible cyclic structure of salmine.** H. FRAENKEL CONRAT and H. S. OLCOTT *Western Regional Research Lab.,<sup>1</sup> Albany, Calif.* When a technique suitable for the esterification of protein carboxyl groups (J. Biol. Chem. 161: 259, 1945) was applied to salmine sulfate (Eli Lilly Co.), negligible amounts of methoxyl (0.06 per cent) were introduced. The absence of free carboxyl groups was also shown by titration from pH 6.0 to pH 2.0 according to the method proposed by Herriott *et al.*

(J. Gen. Physiol. 30: 185, 1946). Protamine sulfate required considerably more acid than the blank but the amount was of the same order as that needed for an equivalent amount of methyl guanidine sulfate. (This observation throws doubt on the suitability of the method for the routine determination of protein carboxyl groups.)

Salmine is known to contain no amino or imino nitrogen (Kossel and Gavrilow, Z. Physiol. Chem. 81: 274, 1912; Waldschmidt-Leitz *et al.*, *ibid.*, 197: 219, 1931). In agreement, the present preparation contained less than 0.1 per cent amino nitrogen by the ninhydrin method, approximately 0.1 per cent by the Van Slyke manometric procedure (3 minutes), and approximately 0.11 per cent by formal titration. These values may reflect guanidyl group reactions. If they and the methoxyl analyses actually measure end groups they would indicate minimal molecular weights of 12,500 to 50,000. Since salmine is readily dialyzable (Visking tubing), its average molecular weight is probably less than 10,000. The data thus suggest that salmine lacks end groups, and that it may have a cyclic structure similar to those suggested for gramicidin and tyrocidine.

**Dye reduction by chloroplast suspensions as a means of measuring their activity for photosynthetic oxygen evolution.** C. S. FRENCH, R. W. SMITH (by invitation) and F. D. H. MACDOWALL (by invitation) *Univ. of Minnesota, Minneapolis, Minnesota*. Illuminated suspensions of chloroplasts or of their fragments may split water with the evolution of  $O_2$  in the presence of a suitable hydrogen acceptor such as the dye phenol indophenol which simultaneously becomes reduced to the leuco form. This reaction is presumably catalyzed by those components of green leaf chloroplasts that are concerned in the evolution of  $O_2$  by normal photosynthesis. Measurements of the velocity of such dye reduction have been made by the use of a photocell mounted behind the reaction vessel. White light completely illuminates the reaction vessel while a diaphragm and a green transmitting filter combination limit the light on the photocell to the beam which has passed through the center of the vessel, and to the spectral region that is most strongly absorbed by the red dye. For a constant concentration of the light scattering chloroplast suspension the log of the photocell response is a linear function of the dye concentration. At the higher chloroplast or dye concentrations the reaction becomes zero order with respect to the dye while at lower concentrations of either it approaches first order. The reaction is not inhibited by 0.01 M KCN nor by 0.001 azide at pH 6.5.

**Studies in endocrine regulation of protein synthesis with isotopic amino acids. I. Hyperinsulinism.** FELIX FRIEDBERG (by invitation), HAROLD TAYLOR (by invitation) and DAVID M.

<sup>1</sup> Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

GREENBERG *Division of Biochemistry, Univ of California Medical School, Berkeley* The rate of incorporation of amino acids into protein can be studied directly if isotopically labeled amino acids are available. In the present study, methionine containing radioactive sulfur was synthesized, added to a protein hydrolysate (Parenamine-Stearns) and injected into rats by way of the jugular vein. After six hours the animals were sacrificed, the protein was precipitated, digested and analysed for inert sulfur by chemical analysis and for radioactive sulfur by means of the mica window Geiger-Muller counter tube. Thus the specific activity was obtained.

It was found that hyperinsulinism depressed incorporation of sulfur into the protein throughout the entire animal but caused an increased elimination of labeled sulfur as total sulfur and total sulfate into the urine. This may mean either that there is conversion of the carbon chain of the amino acid to carbohydrate or that it is completely catabolized.

It was also observed during this investigation that intestinal mucosa is the most and muscle the least active tissue in incorporating sulfur.

By chemical analysis of amino acids with the ninhydrin-carbon dioxide reaction, it was shown that the amino acids of an intravenously administered protein hydrolysate (Parenamine) are more rapidly removed from the blood and tissues of the insulin treated animal than from those of the normal animal. Urinary urea analyses, however, gave no clues to the explanation of the lower amino acid levels in animals with hyperinsulinism.

**Nucleotide and nucleic acid content of human tissues.** MAX M. FRIEDMAN and ALFRED ANGRIST (introduced by Kurt G. Stern) *Dept of Chemistry, Polytechnic Inst., Brooklyn, and Queens General Hospital, Jamaica, N. Y.* Low molecular weight nucleotides may be extracted from finely divided tissues by cold five per cent trichloroacetic acid (acid-soluble phosphorus fraction), whereas polynucleotides of the type of pentose and desoxy-pentose nucleic acid require hydrolysis in this solvent at 90°C for complete extraction (Schneider, W. C., *J. Biol. Chem.* **161**: 293 (1945)).

Analyses performed on human liver, obtained at autopsy, by this procedure yielded values for total pentose and desoxypentose nucleic acid comparable to Schneider's data for rat liver. However, the ratios of material, extractable with trichloroacetic acid at 60 and 90°C respectively, varied significantly with the age of the individuals studied, both with regard to the pentose and desoxypentose polynucleotide fractions. Relatively larger amounts of both types of nucleic acids were found to be soluble in this solvent at the lower temperature in the instance of individuals averaging ten years of age than in the case of individuals averaging 73 years

of age. The total polynucleotide content, on the other hand, appears to be independent of the age.

In a limited number of determinations, the total desoxypentose, but not the pentose nucleic acid content, of several metastatic liver tumors and a hepatoma, as well as several cirrhotoses and two fetal livers, was found significantly increased when calculated on a fresh tissue basis. The nucleic acid fractions found in the pathologic livers also showed a relatively elevated solubility in trichloroacetic acid at 60°C as compared to 90°C, independent of age and comparable to fetal liver and the young age group.

**Metabolism experiments with antimetabolites.** OLIVER H. GAEBLER and E. V. HERMAN (by invitation) *Henry Ford Hospital, Detroit*. Antagonists of niacin, pyridoxine, and pantothenic acid were tested for possible effects on weight, nitrogen balance, glycosuria, and certain blood constituents. The compounds used were pyridine-3-sulfonic acid (PS), 2,4-dimethyl-3-hydroxy-5-hydroxymethyl pyridine (DP), and pantooyl-tauryl-chloroanilide (PT).

In a normal dog which had received a niacin deficient diet for 21 days, adding 0.5 gram of PS to the ration daily caused no abrupt changes in weight or nitrogen balance. No glycosuria developed. Persistent loss of nitrogen only began on the 19th day that PS was fed. Severe blacktongue developed suddenly on the 29th day of PS ingestion, — the 50th day of niacin deficiency. In experiments on 6 litter-mate puppies, 3 received a niacin deficient diet and 3 the same diet plus 0.5 gram of PS per animal per day. The onset and reversibility of deficiency effects was not strikingly different in the two groups.

Results obtained in an insulin-treated depancreatized dog on diets containing subminimal amounts of pyridoxine and pantothenate respectively were as follows: (1) Feeding of 0.5 gram of DP daily for 12 days, and 1.0 gram daily for 12 additional days, increased the fasting blood sugar but did not cause glycosuria. Hemoglobin, cell volume, and serum chlorides were unaffected. (2) Feeding of 1 gram of PT daily was followed, after 3 days, by complete refusal of food. During the 3 days that the food intake remained constant the urine nitrogen rose, while hemoglobin and cell volume fell sharply.

**Fractionation studies of the serum proteins of control and injured goats.** ERLAND C. GJESSING (by invitation) and ALFRED CHANUTIN *Biochemical Lab., Univ. of Virginia*. Goat serum has been fractionated according to the principles formulated by Cohn and his associates. The procedures used for human plasma had to be modified to obtain efficient fractionation and subfractionation. It was found necessary to keep the pH values and the ionic strengths of the serum and supernatants relatively

high in order to prevent the albumin from precipitating

It was possible to isolate electrophoretically pure albumin and two gamma globulins. In addition alpha<sub>1</sub> and alpha<sub>2</sub> globulins were obtained in fairly pure forms. All of these proteins are quite soluble in dilute saline with the exception of the alpha<sub>2</sub> globulin.

The electrophoretic patterns of whole sera of goats injured with vesicants, heat or turpentine showed a definite increase in the beta globulins. This increase is more markedly shown after fractionation.

Fractionation procedures will be outlined and electrophoretic patterns will be shown. [This work was done under contract with the Medical Division, Chemical Corps.]

**The estimation of nicotinic acid in tissues<sup>1</sup>**  
HAROLD C. GOLDBTHORPE and DORIS TIPPIE (introduced by Leo T. Samuels) *Dept. of Biological Chemistry, Univ. of Utah Medical School, Salt Lake City, Utah*. The CNBr procedure of Bandier and Hald<sup>2</sup> has been modified to greatly increase sensitivity and reproducibility. The original method was found to give inconsistent values and off colors were often encountered. A study of the factors involved led to a modification of the procedure with an increase in sensitivity in which quantities of niacin in the order of 1 to 3 micrograms are easily estimated. Recoveries of added niacin, 0.5 to 15 micrograms to pepsin digests of protein and tissues averaged 99.6% (98.4 to 102%) and 99% (97.7 to 100%) respectively. Recovery of nicotinamide added to tissue samples, pepsin digested, followed by alkaline hydrolysis averaged 100.4% (97.8 to 103.5%).

For consistent results the following conditions were noted. The CNBr reagent is best prepared from crystalline CNBr. The temperature for the CNBr reaction must not go above 40°C for 5 minutes, or better, 25°C for 30 minutes of reaction time. The pH of the medium is very critical, color development falls off very rapidly on either side of the pH values of 4.9 to 5.3. The reaction must be conducted in the dark.

The claim as to the stability of the chromogen produced with p-methyl aminophenol sulfate is correct. Only very slight fading was measured when the reactants were left out in room light for four hours. The amine reaction gave increased color development when kept at a temperature of 15°C and allowed to react for 75 minutes.

The method has been applied to the study of the effects of various diets on the niacin content of rat tissues.

**Desamidation of amides in the presence of pyruvate** JOSE M. GONCALVES (by invitation), VINCENT E. PRICE (by invitation), MAURICE ERRELLA (by invitation) and JESSE P. GREENSTEIN *National Cancer Inst., National Inst. of Health, Bethesda, Maryland*. The desamidation of glutamine in aqueous extracts of rat liver is increased by added pyruvate at a pH (6.5) where glutaminase and asparaginase activity are minimal. Pyruvate has no effect on the desamidation of isoglutamine, chloroacetyl asparagine, glycyl asparagine, or benzoylarginine amide. The optimal effect of pyruvate on the susceptible amides is obtained with a ratio of 2 moles of keto acid to 1 of amide. The same effect is noted in digests of the susceptible amides with peptides of cystine or aminoacrylic acid (dehydroalanine) which yield pyruvate on enzymatic degradation.

That the effect of pyruvate is not just an augmentation of glutaminase and asparaginase activity is demonstrated not only by the difference in pH optima, but also by the fact that the activity of these two enzymes is destroyed by heating the extract for 10 minutes at 50°C, a temperature at which the pyruvate effect on the desamidation of the amides is relatively little affected.

**Some amino acid analyses of whole casein,  $\alpha$ -casein and  $\beta$ -casein WILLIAM G. GORDON, and (by invitation) WILLIAM F. SEMMETT, ROBERT S. CABLE and DAVID G. DOHERTY *Eastern Regional Research Lab., Philadelphia 18, Pa.* Separation of casein into two mutually distinct fractions,  $\alpha$ - and  $\beta$ -casein, has been reported by this laboratory (J. Am. Chem. Soc. 66:1725 (1944)). Investigation of the comparative amino acid composition of whole casein,  $\alpha$ -casein and  $\beta$ -casein has revealed some noteworthy differences, as shown in the following table. The amino acid contents are expressed as percentages of dry, ash free protein, each figure being the average of replicate analyses.**

	Whole casein	$\alpha$ Casein	$\beta$ Casein
Lysine	8.1	8.9	6.6
Amino N	0.93	0.99	0.73
Arginine	4.1	4.3	3.4
Histidine	3.1	2.9	3.1
Tyrosine	6.3	8.1	3.2
Tryptophane (A)	1.2	1.5	0.7
Tryptophane (B)	1.3	1.7	0.5

Lysine was determined by Hanke's decarboxylase method (Fed. Proc. 5:137 (1946)), amino nitrogen by Doherty and Ogg's modification of the Van Slyke method, arginine and histidine by Macpherson's colorimetric procedures on catholytes obtained by ionophoresis, tyrosine and tryptophane (A) by Brand and Kassell's methods, and tryptophane (B) by Shaw and Macfarlane's method.

<sup>1</sup> Aided by grants from the Research Fund of the University of Utah and the Sugar Research Foundation.

<sup>2</sup> Biochem. Jour. 33:264 (1939).

The histidine content of casein and its protein components appears to be about the same, but the other amino acids investigated are present in considerably smaller amounts in  $\beta$ -casein than in the  $\alpha$ -fraction. Analyses of two distinct preparations of  $\alpha$ -casein and two of  $\beta$ -casein for lysine, tryptophane, tyrosine, amino nitrogen and phosphorus indicate that different preparations of the same fraction have a constant and characteristic amino acid composition.

**The maintenance of *L. casei* and *L. arabinosus* cultures in the lyophilized state** WILLIS A. GORTNER and FRANCES E. VOLZ (introduced by L. A. Maynard) *School of Nutrition, Cornell Univ.* Cultures of *L. casei* and *L. arabinosus* were lyophilized by a procedure described previously (Science 102:125 (1945)). The desiccated cultures were stored in the dark at room temperature.

At two-month intervals representative cultures were rehydrated to 2 ml with sterile saline and used directly as inoculum. Niacin standard tubes were used for testing the *L. arabinosus* and riboflavin for the *L. casei*.

The *L. arabinosus* culture maintained its original acid-producing capacity over a 12-month period regardless of the appearance of the lyophilized culture. When the mean acid production of 20 cultures was used to plot a master standard curve, the recovery of niacin calculated for individual cultures from this curve was within the limits of accuracy of microbiological methods.

Acid production by all lyophilized *L. casei* cultures decreased during the first two months of storage, but remained constant thereafter with the exception of those few cultures which initially had a poor appearance.

Transfer of the *L. casei* cultures to media before using them as inoculum increased acid production by about 10 per cent at the 2–3  $\mu$ g riboflavin levels.

The results of the storage study indicate that the lyophile procedure is a simple, economical, and reliable means of maintaining bacterial cultures for microbiological assays. The procedure insures a reproducibility of standard curves, obviates the frequent transfer of the organisms and the preparation of agar and broth media, and enables one to use the culture immediately as inoculum without the customary 24 hour prior incubation.

**Studies with radioactive phosphorus of acid-soluble phosphate changes in hyperthyroidism** DAVID M. GREENBERG, JANE FRAENKEL CONRAT (by invitation) and MARY BETH GLENDENING (by invitation) *Division of Biochemistry, Univ. of California Medical School, Berkeley*. Tracer experiments were performed with radioactive phosphorus on the turnover of the acid-soluble phosphates to study the role of the thyroid in carbohydrate metabolism. It was observed that hyperthyroid activity affected the rate of turnover of  $P^{32}$  in

muscle, liver, and kidney with little or no associated alterations in the total acid-soluble, inorganic, or labile phosphorus fractions.

The  $P^{32}$  content of the total acid-soluble, inorganic and labile phosphorus fractions of liver and kidney was 25 to 50 per cent lower while that of muscle was over 100 per cent greater, 110 minutes after administration, in hyperthyroid than in fasted control rats. In the blood serum of the hyperthyroid rats the inorganic phosphate was increased but the  $P^{32}$  was decreased.

In hypothyroidism it was found that the accumulation of  $P^{32}$  was increased in blood, liver and kidney and decreased in muscle.

Comparison of the ratios of the specific activities of the phosphorus fractions of the three tissues to that of the blood showed that liver had the greatest and muscle the lowest ability to concentrate phosphorus. There was, however, little difference between the liver and kidney in hyperthyroid and control animals in this respect. On the other hand, the ratios of specific activities was much higher for the muscle of the hyperthyroid animals, evidently due to a more rapid uptake of  $P^{32}$ .

The more rapid uptake of  $P^{32}$  by muscle in hyperthyroidism may serve to explain the relative deficiency observed in the blood, liver and kidney. The observed relationships suggest that thyroid activity influences the rate of transfer of phosphorus across cell membranes. [Aided by grants from the John and Mary R. Markle Foundation and the Christine Breon Fund of the University of California.]

**Effect of pH on apparent pK of phenolic groups in protein** G. ROBERT GREENBERG (by invitation) and CYRUS P. BARNUM *Dept. of Biochemistry, Western Reserve Univ., Cleveland and Dept. of Physiological Chemistry, Univ. of Minnesota, Minneapolis*. The presence of diiodotyrosine in iodinated protein can be demonstrated spectrophotometrically by the ultraviolet absorption band of the phenoxide ion which begins to appear at less than pH 7. Phenolic groups of non-iodinated proteins do not exhibit a phenoxide band until the pH is raised to values of approximately 10 or greater depending on the protein. In addition the position and the extinction coefficient of the latter band is considerably different from that of the corresponding band for the phenoxide ion of free diiodotyrosine.

It was found that the apparent pK of the phenolic groups of diiodotyrosine in crystalline bovine serum albumin as determined spectrophotometrically with the Henderson-Hasselbalch equation increased with an increase in pH. This perhaps may be explained as being due to the effect of the changing charge arising from the polyvalent nature of proteins or by differences between the pH at the surface of the protein and that in the solution.

It may be noted that the imidazole group of histidine possesses a hydrogen dissociating in approximately the same pH range as the phenolic hydrogen of duodotryosine

**Growth inhibitory action of amino acids in nicotinic acid-low diets for chicks** A C GROSCHKE, J O ANDERSON, and G M BRIGGS (introduced by V R Ellis) *Dept of Poultry Husbandry, Univ of Maryland, College Park* An earlier study demonstrated that gelatin had a growth-depressing action on chicks when incorporated in a highly purified diet low in nicotinic acid (*J Biol Chem* 161 749 (1945)) This growth depression was later shown to be due largely to the combined action of glycine, arginine and alanine (*J Biol Chem* 165 739 (1946)) In both instances normal growth was obtained upon the addition of nicotinic acid

Similar employment of another tryptophane low protein, zein, produced growth inhibition Feeding an amino acid mixture simulating zein protein likewise had a deleterious effect on growth Correction was obtained with nicotinic acid

Since zein contains no glycine and very little arginine, these amino acids obviously were not primarily involved in the results obtained with this protein This suggested that other amino acids had growth inhibiting potentialities in the absence of sufficient nicotinic acid Accordingly, 17 amino acids were individually tested at a level of 4 per cent under essentially the same experimental conditions as those previously employed Growth depression occurred in each case in the following order (figures indicate growth as per cent of basal gain at 4 weeks) dl methionine (all dead at 4 weeks), l(+) lysine 33, l(+) cystine 34, l(-) proline 43, l(+) arginine 46, l(+) histidine 49, l(-) tyrosine 49, glycine 50, dl alanine 59, l(+) glutamic acid 61, dl isoleucine 65, dl phenylalanine 65, dl aspartic acid 71, dl threonine 71, dl serine 79, l(-) leucine 79, dl valine 80

The effect of nicotinic acid in counteracting these growth depressions will be discussed

**The relation of nitrogen metabolism to the regeneration of liver protein** FRASER N GURD (by invitation), HARRY M VARS and I S RAVDIN *Harrison Dept of Surgical Research, Schools of Medicine, Univ of Pennsylvania, Philadelphia* A large reduction in the liver protein of 250 grams male Wistar rats was achieved by a 14 day period on a non-protein diet, followed by 69.4% hepatectomy Nitrogen balances were determined daily during a standard postoperative period of 14 days, and the amounts of new liver protein measured The following postoperative diets were offered ad libitum to groups of 6 rats each non protein, 5, 10 and 18% casein, alone and with 1% methionine added

Average figures are shown for the net total N balances (A), and for the amounts of new liver

protein formed (B) in the 14 day regeneration period The figures are in grams per 100 gram initial body weight

	Dietary casein (per cent)						
	0	5	5 + M	10	10 + M	18	18 + M
A	-0.25	-0.07	-0.01	+0.25	+0.29	+0.45	+0.54
B	0.17	0.22	0.24	0.30	0.33	0.37	0.42

A close correlation appeared to exist between the amount of new liver protein formed and the amount of N saved or spared, irrespective of whether the rats were in positive or negative N balance It is suggested that any factor, or summation of factors, which causes an overall change in nitrogen metabolism, will affect the liver protein

**The biological conversion of radioactive phenylalanine to adrenalin** SAMUEL GURIN and ADELAIDE M DELLUVA (by invitation) *Dept of Physiological Chemistry, School of Medicine, Univ of Pennsylvania, Philadelphia* dl Phenylalanine labelled with  $C^{14}$  in the carboxyl and alpha positions was synthesized from doubly labelled glycine Rats were given subcutaneous injections of 100 to 300 mgs of substance either in a single dose or once daily for three days Following anesthesia with amytal, the adrenal glands were removed and promptly extracted with dilute acetic acid containing 50 mgs of non radioactive adrenalin which served as a carrier Adrenalin samples were isolated and recrystallized three times from acetic acid and ammonia All of the adrenalin preparations were significantly radioactive Furthermore, oxidation with  $HIO_4$  demonstrated that all of the radioactivity was localized in the terminal side chain carbon of the adrenalin

dl Phenylalanine labelled with tritium ( $H^3$ ) was fed as 1 per cent of the diet to a 150 gram rat for a period of 10 days After isolation and recrystallization of the adrenalin as previously described, a significant amount of tritium was found to be present The concentration of tritium was too high to be accounted for by exchange reactions with body water

The evidence indicates that the biological conversion not only involves decarboxylation of phenylalanine but that the residual aliphatic side-chain remains firmly attached to the benzene nucleus during the biological synthesis of adrenalin

**The role of methylene blue and pyridine nucleotides in the reduction of methemoglobin in hemolyzates** HELMUT R GUTMANN<sup>1</sup> (by invitation), BERNARD J JANDORF and OSCAR BODANSKY<sup>2</sup>

<sup>1</sup> Present address: Dept of Biochemistry Yale University School of Medicine New Haven Conn

<sup>2</sup> Present address: Dept of Pharmacology Cornell University Medical College New York City, N Y

*Biochemistry Section, Medical Division, Edgewood Arsenal, Md* In the absence of added substrates, methylene blue oxidizes hemoglobin in washed intact and laked erythrocytes. In the presence of glucose or lactate and methylene blue, methemoglobin is reduced in intact methemoglobinemic cells but not in water hemolyzates prepared therefrom. If hemolysis is performed in the presence of 0.16 M nicotinamide, methemoglobin is reduced rapidly in the presence of methylene blue and hexose diphosphate or lactate, glucose cannot function as substrate in this system. Reduction is inhibited by 0.001 M iodoacetic acid.

Addition of a partially purified preparation of DPN-H<sub>2</sub> to methemoglobin and methylene blue results in the rapid reduction of methemoglobin, DPN cannot replace DPN-H<sub>2</sub> in this system. Conditions are defined for the action of methylene blue as an oxidant of hemoglobin or as a reductant of methemoglobin.

**Photometric determination of bromsulphalein in hemolyzed, lipemic, or icteric serum** ROBERT HOUSTON HAMILTON (introduced by Howard W. Robinson) *Temple Univ. School of Medicine* The usual procedure for determining bromsulphalein is to measure light transmission in an acidified sample, alkalinize, and measure light transmission again, the difference in transmission being taken as a measure of the concentration of the bromsulphalein present. This procedure gives reasonably accurate results with serum not containing hemoglobin. The light absorption of the latter substance changes in acid and in alkaline solutions, the change producing an error in dye determination.

It has been found possible to eliminate this interference of hemoglobin by adding the serum to an alkaline solution containing hydrazine hydrate, measuring light transmission, bleaching the dye selectively with sodium dithionite, and measuring the light transmission again. By this procedure the hemoglobin is converted to hemochromogen, and remains as this derivative during the subsequent reduction of the dye.

The method is applicable not only in normal and in hemolyzed serum, but also in the presence of lipemia and of bilirubinemia.

**The significance of parathyroid activity in physiological regulation of acid-base balance** PHILIP HANDLER and JOHN MCCOY (by invitation) *Duke Univ. School of Medicine, Dept. of Biochemistry, Durham, N. C.* Parathyroid extract (400 units) was given intravenously to 8 healthy adult males under normal control conditions and after dosage with NH<sub>4</sub>Cl and with NaHCO<sub>3</sub>. Three 60 minute urine specimens were collected before administration of the parathormone and three thereafter.

Urinary phosphate excretion increased under all circumstances and was sustained for the entire

three hour period. However, while the increment in phosphate excretion was slightly lower in the acidotic subjects than under basal conditions, the increment was at least 3 × greater during alkalosis than that under basal conditions in the same subjects.

Administration of parathormone resulted in an immediate elevation in urinary pH of as much as 1.4 pH units with an average of 0.6 units under basal conditions and 0.7 units in the acidotic subjects. However, this was not sustained in either case. Only a slight elevation of pH was observed in the alkalotic subjects whose urine averaged pH 7.8 before parathormone administration. The increment in bicarbonate excretion (expressed in mEq of Na<sup>+</sup> per hour) under basal conditions was of the same order of magnitude as that of phosphate excretion while under alkaline conditions the increment in bicarbonate excretion was greater than that in phosphate excretion.

Parathyroid extracts did not inhibit preparations of carbonic anhydrase. Moreover, the increased alkali excretion induced by sulfanilamide administration was accompanied by diminished phosphate excretion. Further experiments are in progress to determine the significance of parathyroid activity in renal regulation of acid base balance, the role of the circulating level of ionized calcium in this regard and the mode of operation of parathormone in the kidney.

**Tissue storage of mercury following repeated administration of organic mercury diuretics or mercuric chloride** R. N. HARGER, and (by invitation) J. R. BENNET, H. R. HULPIEU, and A. J. SCHNEIDER *Depts. of Biochemistry-Pharmacology and Pathology, Indiana Univ. School of Medicine, Indianapolis, Indiana* *A Dog Experiments* The mercurials studied were mercupurin (I), salyrgan-theophylline (II), and mercuric chloride (III). These were administered in 18 equal doses over a period of 3 weeks. The routes of administration and weights per kilo of total administered mercury were: I and II, intramuscular, (a) 21 mg, and (b) 105 mg, I, oral, (c) 80 mg, and (d) 300 mg, and (e) III, oral, 18 mgs. Two days, or 23 days, after the last dose, the animals were sacrificed and their kidneys, livers, stomachs, and intestines were analyzed for mercury. Blood NPN was also run at intervals. The dogs killed 2 days after the last dose showed the following ranges of kidney mercury concentration, expressed as mg per cent: (a)<sup>1</sup> 1.52-2.52, (b) 7.17-8.48, (c) 1.68-2.24, (d) 2.92-13.00, and (e) 2.15-5.65. With animals killed 23 days after the last dose, the corresponding figures for the kidneys were: (b) 1.38-4.21, (c) 2.62, and (e) 0.97-1.08. The concentration of mercury found in the liver averaged about one-fifth of that

<sup>1</sup> See same letters above for details of dosage etc.



in the kidney, and the concentrations in the stomach and intestine were much below that in the liver. Several of the dogs showed an elevation of NPN, and three that died during the experiments had marked nitrogen retention, with kidney mercury concentrations of 12.20, 7.17, and 8.18 mg per cent. These had received I (b), II (b), and I (c).

**B Human Studies** Mercury analyses were run on kidneys from hospital patients who had received mercupurin therapy. Two cases, which developed high blood NPN, following mercupurin medication, showed kidney mercury concentrations of 17.9 and 8.56 mg per cent. Three other cases, who probably died of simple cardiac failure, had kidney mercury figures of 0.69, 0.93, and 2.95 mg per cent.

The complete paper will contain pathological findings and other details.

**Amino acid excretion in the urine** CECIL C HARVEY (by invitation) and M. K. HORWITZ, *Biochemical Research Lab., Elgin State Hospital, Elgin, Illinois*. A study has been made of the amounts of the essential amino acids in the urine of twenty men on a controlled dietary regime. Amino acid assays were made by microbiological methods. Because of the inhibiting effects on the microbiological techniques of urea, and possibly other substances in the urine, not all of the free amino acid determinations gave valid results. Since the inhibiting effects of urine are destroyed by refluxing with 6N HCL for eight hours, it was possible to do total amino acids on hydrolyzed urine with relative assurance of accuracy. The results obtained indicate that varying amounts of polypeptide substances are present in different individuals and that these amounts can not be related to the larger molecules which can be precipitated with sulfosalicylic acid. The average older individual excreted larger amounts of total amino acids than the average younger individual.

**In vitro observations on  $C^{14}O_2$  incorporation in liver glycogen** A. B. HASTINGS, C. B. ANFINSEN, R. G. GOULD (by invitation), I. N. ROSENBERG (by invitation), and A. K. SOLOMON (by invitation), *Dept. of Biological Chemistry, Harvard Medical School*. Rabbit liver slices have been incubated *in vitro* in a medium containing pyruvate or glucose as substrate and  $NaH^{14}CO_3$  in the presence of various combinations of Na and K ions. The amount of glycogen and the incorporation of  $+4C$  in the glycogen have been determined after a two hour incubation period.

Confirming earlier observations (Buchanan, J. M., Hastings, A. B., Nesbitt, F. B., *J. Biol. Chem.* 145: 715 (1942)),  $CO_2$  incorporation has been found to occur to the extent of approximately 10 per cent of the glycogen carbon with pyruvate as substrate. On the other hand, when glucose is substituted for

pyruvate, the amount of  $+4C$  incorporated is only about 2 per cent.

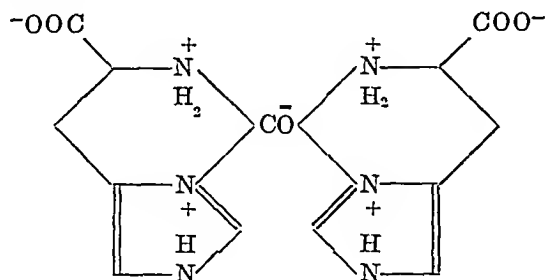
Incubation in a medium, containing Na—72 mM/L, K—73 mM/L, Ca—10 mM/L, resulted in the formation of more glycogen and more  $+4C$  incorporation than incubation in solutions containing either potassium and no sodium, or sodium and no potassium. Much less glycogen was formed in solutions containing Na—145 mM/L, K—0, than in solutions containing K—145 mM/L, Na—0.

Both histological and chemical evidence indicates that essentially all the glycogen present at the end of incubation in whatever medium is newly formed glycogen, whether or not it exceeds the initial value of chemically determined glycogen. [This work was supported in part by a contract between Harvard University and the Office of Naval Research.]

**An in-vitro method for studying various substances upon red cell maturation** EDWIN E. HAYS and ELIZABETH C. PAULSEN (by invitation), *Dept. of Biochemistry, Univ. of Vermont College of Medicine*. Rat bone marrow cells are centrifuged to remove the majority of the mature red cells and the immature cells are then suspended in a glucose-free Tyrode solution. This preparation of cells has been used to study the occurrence of erythrocyte maturing factors in yeast, normal and pernicious anemia human serum, rat serum, and liver extracts. The number of reticulocytes produced after an incubation period of several hours is used as a means of quantitatively evaluating the amount of maturing substance (or substances) present in the solution being tested. Synthetic folic acid, vitamin B<sub>12</sub> conjugate, various amino acids, commercial casein hydrolysate, the B-Complex vitamins, and several purified proteins have been tested and were found to be lacking in the maturation factor. Liver extracts which are inactive with respect to their antipernicious anemia potency likewise do not mature the primitive erythrocytes. Potent antipernicious anemia liver fractions cause a transformation of the immature cells to the reticulocyte stage. Tyrosine, glutathione, and yeast extracts show a small amount of this maturation ability. Serum from pernicious anemia patients in relapse does not have this material present. The maturation substance in normal human serum is stable to freezing and drying, does not dialyze, and is not present in the albumin fraction. [We are indebted to The Armour Laboratories of Chicago, Illinois for the grant that made this work possible.]

**The tetrahedral configuration of cobaltodihistidine** JOHN HEARON (introduced by Dean Burk), *National Cancer Inst., National Inst. of Health, Bethesda, Md.* Cobaltodihistidine is a bichelate compound in which the cobalt is tetraco-

ordinated to the four available amino and basic imidazole nitrogen atoms



An irregular tetrahedral configuration, resulting from the expected covalent hybridization  $d^2sp$ , would involve one unpaired electron. Since, however, the magnetic moment data show that there are three unpaired electrons, it may be concluded that the four nitrogen-cobalt bonds are, like the nitrogen-iron bonds in hemoglobin, essentially ionic in nature. The arrangement of maximum stability for four ionically-bound groups is the tetrahedron.

Supplementary evidence for the tetrahedral structure is furnished by data on rotary dispersion and absorption. Cobaltodihistidine exhibits a band maximum at 4860 Å, which does not occur in solutions of histidine, and is shifted to 5100 Å and much weaker in equivalent cobaltous chloride solutions. The rotation is anomalous, going through a positive maximum ( $[\alpha]^{25} = +221^\circ$ ) at 5400 Å, becoming zero at the band center, and passing through a negative minimum ( $[\alpha]^{25} = -110^\circ$ ) at about 4400 Å (measurements at pH 8.0). The rotation of the *L*-histidine, from which the cobaltodihistidine was prepared, was constant ( $[\alpha]^{25} = -37.2 \pm 0.2^\circ$ ) throughout the range 4200–6600 Å. The Cotton effect here described may be taken as additional evidence that the cobalt is a center of asymmetry and hence tetrahedrally coordinated.

The configuration of oxy-bis(cobaltodihistidine) JOHN HEARON (introduced by Dean Burk) National Cancer Inst., National Inst. of Health, Bethesda, Md. Formulation of the structure of oxy-bis(cobaltodihistidine) must be in accord with (1) the observed stoichiometric ratio 1  $O_2$  : 2  $Co^{++}$  : 4 histidine, (2) the stabilization of the cobaltous state, and (3) the diamagnetic nature of the complex.

The tetrahedral cobaltodihistidine can assume octahedral configuration by acquiring two additional groups. Formation of six covalent  $d^2sp$  bonds by  $Co^{++}$ , through donation of twelve electrons from coordinating groups, necessitates the promotion of a single electron from  $3d$  to  $5s$ . Cobaltous complexes of this type are known to be extremely unstable, especially in the presence of  $O_2$ . Since oxy-bis(cobaltodihistidine) has not been found to be autooxidizable to the cobaltic state, it must be assumed that one single electron from each of the

two cobaltous ions is paired with one single electron from  $O_2$ . The absence of paramagnetism in oxy-bis(cobaltodihistidine) confirms the absence of unpaired electrons, and indicates that the bonds are essentially covalent. Of the three unpaired electrons per  $Co^{++}$ , originally occupying separate  $3d$  orbitals, two have paired when the  $3d$  orbitals are used in covalent bond formation, and the third is paired with a single electron from  $O_2$ , made available by rupturing the two three-electron bonds of the normal  $O_2$  molecule. Thus, each nucleus of the complex is octahedral with six bonds of the  $d^2sp^3$  type: four bonds involving histidine nitrogen, one covalent bond involving  $O_2$ , and one coordinate covalent bond involving  $O_2$ ,  $H_2O$ ,  $COO^-$ , or other available group. Decision on the latter point awaits further data.

A uniform medium for microbiological determination of amino acids with various test organisms L. M. HENDERSON (by invitation) and ESKOND E. SNELL, Univ. of Wisconsin, Madison. A single modified medium containing glucose, sodium acetate, sodium citrate, inorganic salts, adenine, guanine, uracil, xanthine, vitamins and crystalline amino acids has been devised. Under our experimental conditions, using 2 cc total volume, the maximum acid production by various test organisms on this medium after 60–72 hours incubation was equal to or greater than that observed using previously suggested media with *Lactobacillus arabinosus* 17-5, *Lactobacillus casei*, *Lactobacillus delbrueckii* 3, *Lactobacillus delbrueckii* 5, *Leuconostoc mesenteroides* P-60 and *Streptococcus faecalis* R. With these various organisms, and deleting the appropriate amino acid from the medium, satisfactory determinations of fourteen different amino acids in acid hydrolysates of purified proteins have been obtained.

Extensive variations in the concentrations of individual constituents of the medium resulted in no improvements in the standard curve obtained for leucine with three different organisms, as judged by linearity or slope of the curve, or maximum growth response of the test organisms. Blanks were low in all cases. Maximum acid production (with excess leucine) was 80% of the theoretical for *L. arabinosus*, 60% for *L. mesenteroides*, and 50% for *S. faecalis*. The "theoretical" acid production for the medium, which contains 2% of sugar, was considered to be 22 cc of 0.1 N acid per 10 cc of medium.

The medium can be used successfully for turbidimetric as well as for acidimetric assays. A "micro" adaptation of the acidimetric procedure which utilizes a total volume of 0.2 cc has been developed and used successfully in some instances.

Chromatographic separation of cholesterol and cholesterol esters from blood plasma W. C. HESS, Georgetown Medical School. Cholesterol can be

adsorbed from a petroleum ether solution on anhydrous aluminum oxide, prepared according to Brockman, and eluted with a 10 per cent solution of ethyl alcohol in petroleum ether. Cholesterol stearate can be adsorbed similarly and then eluted with 10 per cent ethyl ether in petroleum ether. Mixtures of cholesterol and cholesterol stearate can be separated quantitatively after they are adsorbed on the aluminum oxide column by eluting first with the ethyl ether in petroleum ether followed by the ethyl alcohol in petroleum ether. The procedure was applied to normal blood plasma. Total cholesterol was determined by the method of Schoenheimer and Sperry.<sup>1</sup> Free cholesterol and cholesterol esters were determined by adsorbing a petroleum ether solution of the dried protein free plasma on an aluminum oxide column and eluting with two eluents. The Lieberman-Burchard method was employed directly for the free cholesterol and following saponification of the ester fraction. The sum of the free cholesterol and ester cholesterol was in good agreement with the values found for the total cholesterol. The method is rapid and obviates the precipitation of the free cholesterol as the digtonide. Data will be presented on mixtures of cholesterol and cholesterol stearate and also on a number of normal human blood plasmas.

**Influence of ingestion of single amino acids on the blood level of free amino acids.** STANLEY W. HIER (by invitation) and OLAF BERGEM, *Dept of Biological Chemistry, Univ of Illinois College of Medicine, Chicago, Illinois*. Microbiological analyses for eleven individual amino acids were made on the plasma of dogs following the administration of single amino acids by stomach tube. It was found that there was considerable variation in the rise of blood levels obtained with different amino acids. For example, 60 grams *dl* methionine given to a 12 kg dog caused an increase in the methionine level from 113 mcg per cc to 650 mcg per cc, the level at 24 hours still being high (375 mcg per cc). On the other hand, 25 grams *l* tyrosine given to the same dog gave rise to a maximum tyrosine level in the plasma of only 100 mcg per cc and within 12 hours the level was back to normal. Similar studies were made using ten other amino acids. It was found that ingestion of phenylalanine caused a rise in the plasma level of both phenylalanine and tyrosine, while ingestion of tyrosine increased only the tyrosine. Methionine was found to cause a fall in the level of a number of amino acids, particularly leucine, phenylalanine, lysine and tyrosine.

**Effect of intraperitoneal and subcutaneous administration of particulate materials on body temperatures of albino rats.** ROBERT M. HILL and EDWARD

K. RUTLEDGE (by invitation) *Univ of Colorado School of Medicine*. In 150 adult white rats 5 hours after subcutaneous injection of 2 cc of a 0.1% saline suspension of hydrolyzed yeast, the mean rise in body-temperature was 1.5°C. In 12 rats, 2 cc of india ink gave similar values. The same amount of each of these suspensions injected intraperitoneally produced a decrease in body-temperature. Hydrolyzed yeast produced a mean maximum body-temperature fall of 2.7°C and india ink, 3.1°C. In one instance, 2 cc of india ink produced a maximum fall of 6.4°C, which was reached 28 hours after injection, with return to normal in 48 hours. Suspensions of blood charcoal and of yeast nucleic acid gave similar results. Carmine (4 cc of a 2% suspension) gave a mean maximum body-temperature fall of 3.9°C. Trypan blue behaved similarly to carmine but gave less intense reactions. The much greater solubility of trypan blue seems to be the reason for this difference. Adenine, guanine, xanthine, uracil, allantoin, lipiodol, barium sulfate, milk, and egg albumin were ineffective by either route.

In only a few cases, particularly with india ink, was there any evidence of shock as judged from determinations of plasma protein and red cell volume. During hypothermia, the otherwise quiet animals became normally active when disturbed. In every case so far studied, body-temperature fall has been associated with rapid phagocytosis of the particulate material and its general distribution throughout the reticulo endothelial system.

**The occurrence and isolation of the pneumonia-susceptibility factor.** GEORGE H. HITCHINGS and ELVIRA A. FALCO (by invitation) *The Wellcome Research Laby*. The dietary factor<sup>1</sup> which increases the susceptibility of mice to infection with Type I, SV 1 strain of pneumococcus has been found to occur in a number of foodstuffs. The factor is absent, or nearly so, from yeast, liver, white flour, corn meal and linseed meal. It is present in the following: peanuts, oats, wheat bran and wheat germ, respectively, in the order of increasing concentrations.

The factor, as it occurs in wheat germ, is insoluble in organic solvents and in dilute aqueous alkali, but soluble in dilute acid. A 200 fold concentration of the factor has been accomplished by percolation of wheat germ with 70 per cent aqueous acetone and 0.1 per cent sodium bicarbonate followed by extraction with 0.08 N hydrochloric acid. The acid extract is concentrated to dryness *in vacuo* and the active factor is separated from a small amount of protein by dialysis, and again evaporated to dryness. When 0.5 gram of this concentrate is added to a kilogram of synthetic diet, a marked increase in

<sup>1</sup>Schoenheimer R. and Sperry W. W., *J Biol Chem* 106 745 (1934)

<sup>1</sup>Hitchings G. H. and Falco, E. A., *Proc Soc Exp Biol and Med* 61: 54 (1946)

the susceptibility of mice to pneumococcal infection is observed

**Calcium exchange in bone using radiocalcium in vitro** HAROLD CARPENTER HODGE, MARLENE FALKENHEIM (by invitation) and ELIZABETH EMERY (by invitation) *In vitro* experiments in which powdered bone ash was exposed to solutions of  $\text{CaCl}_2$  (pH 7.4, 5 mg % Ca) containing  $\text{Ca}^{45}$  have shown that bone exchanges calcium with the solution. The  $\text{Ca}^{45}$  concentration on the bone rises to 65 per cent of the total originally in the solution during the first 8 hours' exposure. At this time a 'quasi equilibrium' is reached between the exchangeable bone calcium and the solution. The exchangeable bone calcium represents at the most less than 25 per cent of the total bone calcium, this fraction is of the same order of magnitude as that previously reported for the exchangeable bone phosphate.

When labeled bone (after 9 days adsorption) is exposed to non-radioactive  $\text{Ca}^{40}$  solution, 65 per cent of the bone  $\text{Ca}^{45}$  remains in the bone, indicating the reversibility of the exchange process toward the same quasi equilibrium point.

**Separation and electrophoretic analyses of the proteins of normal dog tissues** ELMORE HOLMES (by invitation) and DENNIS B. MORRISON *Dept. of Chemistry, Univ. of Tennessee, Memphis*. Proteins of heart, skeletal muscle, liver, kidney, and blood plasma were analyzed in the Tiselius-Longsworth apparatus. Dissected tissue was homogenized in a Waring blender. The homogenate was then frozen and thawed after which aliquots were taken for centrifugation (12,000 r.p.m.), for determination of water content, total solids, and proteins (Kjeldahl), and for fractionation of the proteins by extraction. Proteins soluble in 0.12 M NaCl were first removed by repeated extraction. The residue was then similarly extracted with 1.0 M NaCl, and finally with 0.06 M NaOH. Only a small insoluble fraction remained after these successive extractions. All extractions were carried out at 3-5°. Total proteins were determined on each extract, on the final insoluble residue, and on the supernatant obtained by centrifugation (heart and muscle only). The supernatant fluids and saline extracts were also equilibrated against veronal buffer (pH 8.6) preparatory to electrophoresis. During dialysis of the 1.0 M NaCl extracts a large precipitate (liver and kidney) or a clear fibrin-like clot (muscle and heart) formed, thus invalidating subsequent electrophoresis of these extracts.

About 65 per cent of the total protein of glandular tissue (liver and kidney) and 36 per cent of muscle (skeletal and heart) was extractable by 0.12 M NaCl. Electrophoretic analyses were made of the supernatant fluids and the 0.12 M NaCl extracts. Characteristic and reproducible patterns were obtained for each tissue. All tissues exhibit 2 or 3

main components which migrate between the gamma and alpha<sub>1</sub> positions of the blood plasma pattern. All tissues contain a gamma component and a component faster than albumen. Albumen, however, is seen as a distinct component of the proteins from the heart only.

**The isoleucine requirement of the infant** L. EMMETT HOLT, JR., ANTHONY A. ALBANESE, VIRGINIA IRBY (by invitation), SELMA E. SNYDERMAN (by invitation), and MARILYN LEIN (by invitation) *New York Univ. College of Medicine*. The attempt was made to determine the isoleucine requirement of the infant by studying nitrogen retention and growth on a diet deficient in isoleucine. This diet was prepared by using an acid hydrolysate of hemoglobin as the source of nitrogen. Control periods were run with a similar diet supplemented stepwise with l(+)-isoleucine.

Three infants were studied in this manner. It was found that on the isoleucine deficient diet the infants failed to gain weight or lose weight, whereas the isoleucine supplemented diet restored a normal weight gain. Nitrogen retention likewise fell off during the deficiency periods and was restored to normal levels by the addition of isoleucine.

Excellent nitrogen retention and gain in weight were observed with a diet supplying approximately one third of the isoleucine contained in commonly employed milk formulae.

No reduction in total plasma proteins or hemoglobin was induced by a 3 week period of the deficient diet in contrast to similar experiments on a tryptophan deficient diet.

**The formation of methionine from cysteine in Neurospora** N. H. HOROWITZ *California Inst. of Technology*. A large number of mutants of *Neurospora* have been obtained which have lost the ability to synthesize methionine, as shown by the fact that, unlike the wild type, they fail to grow on a medium of inorganic salts, sugar, and biotin, but grow on the same medium supplemented with methionine. Four mutants were selected for the present study. Strains 39816, 36104, and H98 can utilize homocysteine in place of methionine, while strain 38706 cannot, even when supplied extracholine or betaine, indicating that the ability to methylate homocysteine has been abolished in the latter strain. Strain 39816 utilizes cysteine, as well as homocysteine or methionine, showing that cysteine synthesis is blocked in this mutant and that methionine can be formed from cysteine in *Neurospora*. The results further indicate that homocysteine is an intermediate in this conversion. Strains H98 and 36104 are unable to convert cysteine to homocysteine. Closer study showed that a substance capable of supporting growth of strains 39816 and 36104, but not of 38706 or H98, accumulates in growing cultures of strain H98. The substance has been isolated from cultures and has been

identified is *l*(+) cystathionine,  $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-S-(CH}_2\text{)}_2\text{-CH(NH}_2\text{)-COOH}$ . Identification was made on the following criteria: elementary analysis, specific rotation, decomposition temperature, melting point of the dibenzoyl derivative, and biological activity is compared with that of synthetic *l*(+) cystathionine furnished by Prof. du Vigneud. These results indicate that *Neurospora* converts cysteine-S to methionine-S by the following series of gene controlled steps: cysteine  $\rightarrow$  cystathionine  $\rightarrow$  homocysteine  $\rightarrow$  methionine.

**Biochemical changes in the blood following electric shock therapy.** WILLIAM A. HORWITZ (by invitation) and WARREN M. SPERRY, *Depts. of Psychiatry and Biochemistry, New York State Psychiatric Inst. and Hospital*. It was previously reported (Horwitz, Sperry, and Barrera, *Proc. Am. Psychiat. Assoc.*, p. 28 (1943)) that a sharp rise in the cholesterol, phosphatide, and protein concentrations of the blood serum occurs within 1 to 2 minutes after a grand mal convulsion induced by electric shock. Since the increase, which varied from approximately 7 to 20 per cent, was usually about the same for each of the three constituents, it was concluded that an equivalent proportion of water had been withdrawn from the blood serum. In petit mal reactions induced by electric shock cholesterol, phosphatide, and protein concentrations decreased immediately after the seizure. During the ensuing hour the concentrations usually returned to the pre-treatment level and, in many cases of the grand mal type, even reached considerably lower values.

In further studies similar changes have been found after electric shock superimposed on insulin shock and after spontaneous seizures during insulin shock, but in a few instances there was a lack of parallelism between the responses of cholesterol and phosphatides. When curare was administered just before a convulsion caused by electric shock the increase in cholesterol and phosphatides was usually decreased or abolished, and here also the behavior of the two lipids was not always the same. There is some indication of a relationship between the pattern followed by the blood lipids after a convulsion induced by electric shock and the subsequent clinical progress of the subject.

**The assimilation of amino acids by respiring washed staphylococci.** ROLLIN D. HORCHAKISS, *Rockefeller Inst. for Medical Research*. Staphylococci appear to be incapable of synthesizing amino acids, since a complete synthetic growth medium for this species contains most of the  $\alpha$  amino acids. Washed suspensions, however, are able to oxidize many of the amino acids to ammonia, a dissimilation in which the nitrogen is not conserved by the cell.

When amino acids are supplied to washed staphylococci together with an oxidizable substrate such as glucose, the amino acids are not degraded

to ammonia but are incorporated into the cells. The amount of nitrogen so assimilated can approach one fourth the cellular nitrogen content. Nevertheless, the staphylococci are not actually proliferating, inasmuch as other requirements for growth are lacking. Under some conditions polypeptides are liberated into the suspending medium during the process, but it appears that these are waste or exchange products rather than direct products of peptide synthesis.

With the energy provided by glucose oxidation, washed staphylococci are able to esterify and accumulate considerable quantities of inorganic phosphate from the external environment. When amino acids are added to this energy liberating system, phosphate uptake is diminished and nitrogen is accumulated instead. When amino acids are added in mixtures increasing from single compounds to combinations of fifteen or more, there is generally observed a progressive increase in nitrogen uptake and a corresponding decrease in phosphate uptake as the mixture becomes more "complete." 2,4-Dinitrophenol, which inhibits the uptake of inorganic phosphate by respiring staphylococci, without preventing the respiration itself, also inhibits the assimilatory uptake of nitrogen.

**A defect in oxidative phosphorylation in nutritional muscular dystrophy.** JOHN P. HUMMEL (introduced by H. A. Matill), *Biochemical Lab., State Univ. of Iowa, Iowa City*. The normal coupling of oxidation and phosphorylation is markedly depressed in skeletal muscle of hamsters and guinea pigs made dystrophic by tocopherol deficiency. With  $\alpha$ -glycerophosphate as substrate in the presence of adenosinetriphosphate, cozymase, nicotinamide, creatine, cytochrome c,  $\text{K}^+$  and  $\text{Mg}^{++}$ , phosphate buffer, and fresh muscle homogenate, about one mole of phosphocreatine was normally formed per atom of oxygen consumed or per  $2\frac{1}{2}$  moles of lactic acid formed anaerobically with added pyruvate. Addition of fluoride ( $1.3 \times 10^{-3}$  M) reduced the phosphocreatine and lactic acid formation by more than half, oxygen consumption was reduced to a lesser extent.

With dystrophic muscle homogenates, the phosphocreatine synthesis was greatly diminished under both aerobic and anaerobic conditions although the oxygen consumption was only slightly depressed. Lactic acid formation was somewhat smaller but compared with phosphocreatine formation the efficiency of oxidative phosphate transfer was much decreased. Addition of fluoride lowered the phosphocreatine synthesis still further but had little effect on lactic acid formation or oxygen consumption. Muscle degeneration, observed histologically, paralleled the decreased oxidative phosphorylation.

In vitro additions of  $\alpha$ -tocopherol phosphate had no effect on either normal or dystrophic systems. A similar comparison of normal and dystro-

seen in the spectra of 17-ketosteroids was displaced to 1751-1754  $\text{cm}^{-1}$

A comparative study of the spectra of some 140 steroids in carbon disulfide solution has shown that the exact position of the carbonyl absorption band is closely dependent on the position of the carbonyl group or groups relative to the sterol ring system

**Minimum protein and amino acid requirement for maintenance of nitrogen equilibrium in dogs**  
C F KADE, JR (by invitation), J HOUSTON (by invitation), Wm A PHILLIPS (by invitation) and M SAHYUN *Biochemical Research Laby, Frederick Stearns and Co, Division of Sterling Drug Inc, Detroit, Michigan* The mixture in which the proportion of amino acids most nearly approaches the quantitative requirements of the animal should maintain positive balance at the lowest level of nitrogen intake

Nitrogen balance studies were made on adult female dogs to determine the minimum quantity of nitrogen, in the form of certain proteins and amino acid mixtures, necessary to maintain positive balance The animals were given 75 calories/kilo of body weight of a practically nitrogen-free diet, supplemented with either proteins or amino acid mixtures as the sole source of nitrogen It was found that a total nitrogen intake of 140 mg, 110 mg, and 90 mg/kg of body weight as casein, fibrin, and lactalbumin, respectively, will maintain positive nitrogen balance in dogs If the casein is supplemented with 35 mg methionine/kg of body weight, dogs will remain in equilibrium when only 90 mg N/kilo of body weight is ingested Thus, casein, when supplemented by its limiting amino acid, is as satisfactory for maintenance of nitrogen balance in the dog as lactalbumin

Two hydrolysates of casein (one prepared by acid and the other by enzymatic digestion) were studied to maintain positive nitrogen balance, 140 mg N/kilo of body weight of enzymatic hydrolysate "A", and 150 mg N/kilo of body weight of acid hydrolysate "B" fortified with tryptophane is required However, the latter hydrolysate supplemented with sufficient methionine maintains positive nitrogen balance when only 100 mg N/kilo of body weight is fed, indicating that methionine is still the limiting amino acid in the utilization of the mixture

**The mechanism of enzymatic acetylation**  
NATHAN O KAPLAN (by invitation) and FRITZ LIPMAN *Biochemical Research Laby, Massachusetts General Hospital, Boston* In experiments with crude extracts the essential mechanism of acetylation with ATP as a condensing agent—e.g., of sulfanilamide in liver and of choline in brain—is greatly obscured by overlapping reactions A relatively large breakdown of ATP compares with a minute yield in acetylation It has been tried, with

partial success, to fractionate such extracts Between 30 and 66% saturation with ammonium sulfate a protein fraction was obtained from pigeon liver which contains the acetylating system largely isolated from interfering reactions In this system, acetate is the only acetyl precursor, citrate which may stimulate in the cruder extracts and which was suggested as acetyl donor proved inactive

In the purified enzyme system, ATP is rather stable A considerable effect of acetate, coenzyme A (the coenzyme for acetylation), and sulfanilamide on ATP metabolism may now be recognized 0.7  $\mu\text{M}$  ATP- $\text{P}_i$  was split, with either acetate or coenzyme alone, 1.5  $\mu\text{M}$  with both together, with both plus sulfanilamide 1.9  $\mu\text{M}$  ATP- $\text{P}_i$  was split and 0.6  $\mu\text{M}$  sulfanilamide acetylated The coupling of ATP and acetate metabolism in acetylation is further emphasized by the general role of coenzyme A in these reactions The same coenzyme is a factor in the enzymatic formation of acethydroxamic acid with ATP and hydroxylamine, due most likely to intermediary phosphorylation of acetate These observations seem to suggest a more extensive function of the coenzyme in  $\text{C}_2$ -metabolism and may explain the universal presence of the coenzyme [Supported by a grant from the Commonwealth Fund]

**Effects of oxidized lipids in the diet of the rat**  
BRUCE KENNELLY (by invitation) and F W QUACKENBUSH *Dept of Agricultural Chemistry, Purdue University* Fresh and oxidized lard and corn oil were fed to weanling rats in amounts equivalent to 15 per cent of the basal diet which consisted of casein, dextrin, yeast, salts and Cellufour The oxidized lipid was prepared by passing dry air through it in one liter round bottom flasks at 40°C until peroxide values of 100 to 150 were obtained

When vitamins A and E were fed in fresh corn oil mixed with the diet containing oxidized lard, the rats grew briefly then lost weight, developed anemia, showed lack of coordination and died at an average age of 84 days They did not develop typical xerophthalmia However, if given a vitamin A and E supplement by dropper at the time growth ceased, they recovered rapidly

When vitamins A and E were fed in fresh corn oil separately from the basal diet containing oxidized lard or corn oil, growth rate, reproduction and life span were still subnormal However, when the oxidized lipid was not mixed with the basal diet, but fed separately before a three hour fast, the growth rate, reproduction and life span were equivalent to that obtained with fresh lard Reproduction with this diet was inferior to that of the stock colony

The evidence suggests that the reported "toxic" effects of oxidized lipids result from destruction of dietary essentials rather than from a direct toxic action on the animal

**Complex nature of soybean lipoxidase** MARIAN W KIES (introduced by A K Balls) *Enzyme Research Laby, Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, USDA, Albany, California* The oxidation of carotene by lipoxidase and unsaturated fat has been ascribed to a coupled reaction between fat and carotene which occurs at the instant of peroxide formation (Sumner and Sumner, J Biol chem 134 531 (1940)) It was assumed by most workers in the field including ourselves that a single enzyme was responsible for the complete reaction It now appears that so called lipoxidase consists of at least two factors Lipoxidase heated to 70° for two minutes lacks the ability to oxidize carotene when the fat used is peroxide free ethyl linolate, although it still attacks the fat However, when linoleic acid replaces the ester, the carotene is oxidized after a definite incubation period When autoxidized acid or ester is used, the carotene destruction begins immediately The utilization of preformed fat peroxide to oxidize carotene is not a typical peroxidase action, hydrogen peroxide cannot replace the oxidized fat and the reaction is not inhibited by cyanide

The oxidation of linoleic acid alone, measured by peroxide formation, is associated with the stable enzyme preparation, but there is no observable lag in this reaction Both preparations produce the same changes in the ultra violet absorption of linoleic acid All enzymatic activity in lipoxidase is destroyed in two minutes at 80°C

**Inhibition of d-amino acid oxidase by kojic acid** J RAYMOND KLEIN and NORMAN S OLSEN (by invitation) *Depts of Psychiatry and Biological Chemistry, Illinois Neuropsychiatric Inst, Univ of Illinois College of Medicine, Chicago* Kojic acid (5 hydroxy-2 hydroxymethyl-pyrone) inhibits the rate of oxidation of d amino acids by broken-cell preparations of kidney and liver and by extracts of acetone-dried kidney The kojic acid appears to compete reversibly with the substrate for the d-amino acid oxidase The degrees of inhibition by 0.0001 M kojic acid, benzoate, atabrine, and quinine, using the kidney extract and 0.06 M dl-alanine as substrate, were 0.51, 0.28, 0.05, and 0.04 respectively The rates of oxidation of 0.03 M dl-alanine, dl phenylalanine, l(-)-tyrosine, and vanthine by the liver preparations were inhibited respectively 100, 100, 5, and 80 per cent by 0.002 M kojic acid, the oxygen uptake of the liver preparations alone being inhibited about 20 per cent [The kojic acid was kindly supplied by Dr Frank M Stodola]

**Creatinase activity of a strain of pseudomonas** PAUL H KOPPER (by invitation) and HOWARD H BEARD *Depts of Pathology and Bacteriology and Physiological Chemistry, The Chicago Medical School, Chicago, Illinois* Organisms closely re-

sembling *Pseudomonas aeruginosa* were isolated from a "creatinine enzyme" obtained by one of us from human urine<sup>1</sup> When cultivated on a creatinine urine agar medium highly concentrated suspensions of the organism displayed marked creatinase activity *Pseudomonas* creatinase is capable of breaking down 21 mg of creatinine and 17 mg of creatine per hour End products of decomposition of creatine and creatinine include urea, ammonia and carbon dioxide The enzyme cannot be extracted from the bacterial cells with distilled water It differs from Dubos and Millers' NC enzyme in that it acts in the absence of oxygen though the rate of decomposition of creatinine is retarded<sup>2</sup> Evidence was obtained to indicate that the enzyme first converts creatinine to creatine and then proceeds to hydrolyze the latter into urea and presumably sarcosine, which is further broken down to ammonia, carbon dioxide and other unidentified products Glycoeyamidine is readily destroyed by the enzyme Its conversion into glycoeyamine and subsequent slow breakdown of the latter, analogous to that of creatine, are indicated by the results of some of our experiments However, the data obtained so far do not present conclusive evidence to that effect Hydantoin is not attacked at all

**Electrophoretic patterns of plasma from normal and sick children** ELIZABETH L KNAPP (by invitation) and JOSEPH I ROUTH *Depts of Biochemistry and Pediatrics, College of Medicine State Univ of Iowa, Iowa City* Plasma for analysis was obtained from healthy and sick children After dilution with 3 volumes of buffer (0.1 N sodium diethylbarbiturate, pH 8.6, ionic strength 0.1) plasma was dialyzed at 5°C for 3 days with daily change of buffer Electrophoresis was conducted at 0.8°C in the Longworth modification of the Tiselius apparatus

The concentrations of the protein components in plasma obtained from normal children exhibit a fair degree of uniformity In comparison with values for plasma from normal adults, albumin,  $\alpha_1$  and  $\alpha_2$  globulin represent a slightly higher proportion of the total plasma proteins The  $\beta$  globulin component is only about one half that of the adult, whereas the fibrinogen and  $\gamma$  globulin fractions are nearly the same

Electrophoretic patterns of plasma from sick children show considerable variation from the normal, especially in nephrosis The concentration of the protein components from the plasma of 5 nephrotic children (age 3-5) showed good agreement with those obtained by chemical methods The patterns demonstrated extensive alterations in the region of the  $\alpha_2$  and  $\beta$  globulin components

<sup>1</sup> Beard, H H in press

<sup>2</sup> Miller, B F and Dubos, R, J Biol Chem 121 429 447 457 1937



and  $\gamma$  decrease in albumin. The urine from these patients gave evidence for the excretion of  $\alpha_1$  and  $\beta$  globulins in addition to albumin.

Children with rheumatic heart disease (age 7-14) exhibited plasma patterns in which the albumin was definitely lower, fibrinogen,  $\beta$  and  $\gamma$  globulin definitely higher than normal. Interesting variations from the normal patterns were obtained in children with nephritis and nutritional edema.

Biochemical studies on highly purified preparations of influenza A and B viruses. C. A. KNIGHT, *The Rockefeller Inst for Medical Research, Princeton, New Jersey*. Highly purified preparations of influenza A virus (PR8 strain) and influenza B virus (Lee strain) were obtained from allantoic fluids of infected chick embryos by a combination of the methods of differential centrifugation and adsorption on and elution from chicken red cells. Such preparations consisted of particles which were highly active biologically and which were uniform in size, in electro-chemical behavior and in serological reactions. The virus particles of both types of influenza were found to be composed of protein, lipid, ribonucleic and deoxyribonucleic acids, and a polysaccharide containing mannose, galactose and glucosamine units. Microbiological assays for amino acids were made on hydrolysates of 4 to 5 preparations of each of the two strains of virus. The results of the assays indicated that these strains of influenza virus contain approximately the same amounts of alanine, aspartic acid, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, and valine. However, significant differences were found in the values for arginine, glutamic acid, lysine, tryptophane, and tyrosine. It is believed that these differences provide, at least in part, a chemical explanation for the well established lack of immunological relationship between PR8 and Lee influenza viruses.

Molecular sublimation and distillation of cholesterol and its esters. ALFRED E. KOEHLER and ELSIE HILL (by invitation), *Santa Barbara Cottage Hospital and the Sansum Clinic Research Foundation, Santa Barbara, California*. The apparatus consisted of a long closed tube on the inside of which a film of the lipid was deposited. On the inside and concentric with this tube was a water cooled condensing chamber a distance of 0.6 cm from the distilling surface. The outer tube was surrounded by a boiling vapor jacket permitting a wide range of distilling temperatures depending upon the choice of liquid. The distillations were done at 0.05 micron Hg for thirty minutes.

Cholesterol and its esters of the lower boiling fatty acids sublime well below their melting points. The temperature  $^{\circ}\text{C}$  at which 50 per cent distills is as follows: Cholesterol 76, acetate 56, propionate

57, butyrate 65, blood serum esters 123, palmitate 124, and stearate 129.

The sublimation curves for a commercial cholesterol and purified serum cholesterol were identical.

Cholesterol sublimed completely at  $95^{\circ}\text{C}$  but no serum cholesterol esters distilled at this level. This permits a separation of free cholesterol and its esters that agrees favorably with the digitonin method.

Fractional distillation of serum esters after digitonin precipitation indicated a remarkable constancy of the composition of the esters in normal and a variety of disease conditions. However, certain serum esters gave fractionation curves that indicate a greater percentage of the longer chain fatty acids. The presence of such more insoluble esters in the body may be of importance in the deposition of the esters in the blood vessel wall. The possibility that variation in the amount or composition of the serum lipids may effect the distillability of the esters has not been ruled out.

Spectrophotometric studies on the decarboxylation of  $\beta$ -ketoacids. ARTHUR KORNBERG<sup>1</sup> (by invitation), SEVERO OCHOA, and ALAN H. MEHLER (by invitation), *Depts of Pharmacology and Chemistry, New York Univ College of Medicine*. Krebs observed that the spontaneous decarboxylation of oxaloacetic acid is catalytically accelerated by cations such as  $\text{Cu}^{++}$ ,  $\text{Fe}^{++}$ ,  $\text{Fe}^{+++}$ , and  $\text{Al}^{+++}$ , (Biochem J 36 303, 1942). Ochoa and Weisz-Tabori found that oxalosuccinic acid behaves in the same way (J Biol Chem 159 245, 1945).

Although  $\text{Mn}^{++}$  has by itself little effect in catalyzing the decarboxylation of the above ketoacids, their specific carboxylases require  $\text{Mn}^{++}$  for activity, (Kramptitz & Werkman, Biochem J 35 595, 1941; Evans, *et al*, J Biol Chem 147 771, 1943; Ochoa and Weisz-Tabori).

Spectrophotometric measurements suggest that, in the case of oxalosuccinic carboxylase, the main role of the enzyme protein consists in the formation of a protein oxalosuccinate- $\text{Mn}^{++}$  complex which undergoes decarboxylation at a rate proportional to its concentration.  $\text{Al}^{+++}$  has sufficient affinity for the ketoacid so that a complex (which decarboxylates rapidly) is readily formed in the absence of a specific protein. Each of these complexes has a characteristic absorption spectrum in the ultraviolet.

Oxaloacetic acid and its carboxylase behave in a similar manner, but here the enzyme protein also seems to accelerate the decarboxylation of the ketoacid- $\text{Mn}^{++}$  complex. [Supported by grants from the U. S. Public Health Service, The Rockefeller Foundation, The American Philosophical Society, and The American Cancer Society.]

<sup>1</sup> Division of Physiology, National Institute of Health, U. S. Public Health Service.

Factors which influence the stability of tryptophane during the hydrolysis of proteins in alkaline solution K A KUIVEN (by invitation) and CARL M LIMAN *Texas Agricultural Experiment Station, A & M College of Texas* When pure tryptophane was autoclaved in 3 or 4 N NaOH for various lengths of time, a part of the tryptophane was always destroyed The extent of destruction was variable and appeared to have no consistent relationship to the length of time of autoclaving Mixtures of pure amino acids patterned after typical protein hydrolysates afforded partial protection On testing the amino acids separately it was found that the protective action was due to cystine and methionine It was found that the destruction could be completely prevented by the use of cysteine Cysteine was found to exert the same protective action on tryptophane during the hydrolysis of proteins and foodstuffs by autoclaving with NaOH

A study of the mechanism of the protective action of cysteine resulted in the following findings

1 The addition of small amounts of copper salts greatly increased the loss of tryptophane during autoclaving

2 The addition of cysteine resulted in complete stabilization of tryptophane even in the presence of added copper salts

3 Tests with the Warburg apparatus showed that tryptophane dissolved in 4 N NaOH slowly consumes oxygen even at room temperature

4 The rate of oxygen consumption was greatly increased by the addition of small amounts of copper salts Nickel and platinum salts also showed some accelerating effect

5 Cysteine dissolved in 4 N NaOH consumed oxygen at a rapid rate

These findings suggest that the loss of tryptophane which occurs during autoclaving is a result of oxidation catalyzed by heavy metals The function of cysteine in stabilizing tryptophane is probably a matter of rendering the solution oxygen free [Aided by a grant from the American Meat Institute]

A rapid photoelectric method for the determination of serum magnesium H O KUNKEL (by invitation) and P B PEARSON *Nutrition Lab., Agricultural Experiment Station and School of Agriculture, A & M College of Texas, College Station* A rapid method has been developed which permits the determination of serum magnesium without removal of the calcium or precipitation of the magnesium

To one volume of serum add two volumes of water, one volume of 10 per cent sodium tungstate followed by one volume of 0.67 N sulfuric acid Mix thoroughly and filter using a Whatman No. 41 filter paper An aliquot of 3 to 5 ml of the filtrate is transferred to a 10 ml volumetric flask and

carefully neutralized with 0.1 N NaOH, using one drop of 0.01 per cent methyl red as an indicator Then add successively one ml of a 1.0 per cent solution of hydroxylamine hydrochloride, one ml of a 0.063 per cent aqueous solution of titan yellow and two ml of 1.5 N NaOH Make up to volume and bring to a temperature of approximately 25° The red color lake is read either colorimetrically or spectrophotometrically at a wave length 525 millimicrons A blank is prepared without the filtrate and treated exactly as the unknown A standard calibration curve is prepared with magnesium sulfate at levels ranging from 10 to 50  $\mu$ g of magnesium

The intensity of the color is stable, reproducible and follows Beer's law within the limit of the solubility of magnesium hydroxide The recovery of added magnesium to 12 different samples of serum was 99.8 per cent with a standard deviation of 1.6 per cent The method is also suitable for the determination of magnesium in whole blood

Attempts to identify a new crystalline protein from beef pancreas as a proteolytic zymogen M LASKOWSKI, ANNA KAZENKO (by invitation), and CECILIA K KEITH (by invitation) *Dept. of Biochemistry, Marquette Medical School, Milwaukee* Recently described new crystalline protein from beef pancreas (*J Biol Chem* 166:555, 1946) which showed high thymonucleodepolymerase activity was found to exhibit also a proteolytic activity (*J Biol Chem* in press)

Three thousand parts of this crystalline protein were treated with one part of crystalline trypsin and left at 5°C at pH 7.6 The proteolytic activity of our crystalline protein was considerably increased after only a few hours The highest value thus far observed was a five-fold increase after 60 hours The proteolytic activity of the control kept under identical conditions remained unchanged The nucleolytic activity was rapidly destroyed in both experimental and control tubes at this pH No proteolytic activation was observed with crystalline chymotrypsin, but considerable activation was seen after treatment with an aqueous extract of duodenal mucosa The last procedure resulted in slowing down the destruction of the nucleolytic activity

The results of these experiments suggest (1) that our crystalline protein is a zymogen of a proteolytic enzyme, (2) that its proteolytic activity is not of the trypsin type, because no self-activation occurred No definite statement can be made regarding possible similarity to the chymotrypsin type [Aided by grants from the John and Mary R Markle Foundation and the Donner Foundation]

Crystallization of tobacco mosaic virus by serum albumin MAX A LAUFFER *Univ. of Pittsburgh* Tobacco mosaic virus (TMV) can be crystallized

by bovine serum albumin (BSA) when the pH is alkaline to the isoelectric points of both proteins or when the medium is acidic to both isoelectric points

At constant pH the product of the BSA concentration and the electrolyte concentration required to just cause precipitation of the virus was essentially constant. Less albumin and electrolyte were required to cause precipitation at pH 5.8 than at pH 5.2. The precipitate was in the form of mesomorphic fibers which could be transformed into typical rod-shaped virus crystals by the addition of ammonium sulfate. The precipitation of the virus seemed to be essentially complete, and chemical analyses failed to yield evidence of any considerable amount of BSA in the precipitate.

When the pH of the medium was intermediate between the isoelectric points of BSA and TMV, at low ionic strengths a precipitate, which could be dispersed by the addition of sodium chloride, was obtained.

The crystallization under conditions of like charge may be a phenomenon similar to the crystallization of TMV by negative hydrophylic colloids, such as heparin, starch, gelatin, etc., described by Cohen. It may be the result of the virus being literally pushed out of solution by the like charged but more soluble serum albumin particles. The precipitation under conditions of unlike charge is similar to the findings of Kleczkowski, who ascribed the reaction to the formation of compounds with salt linkages. [Aided by the National Foundation for Infantile Paralysis, Inc.]

**Studies on adrenocortical function in relation to lymphatic leukemia.** LOUIS LEVIN<sup>1</sup> *Dept of Hematology, Michael Reese Hospital.* A variety of experimental evidence indicates a relationship between adrenocortical activity and function of lymphoid tissue. The present study was begun to investigate the possible participation of the adrenal cortex in the syndrome of lymphatic leukemia. Two indices of adrenocortical function were studied, (a) adrenal cholesterol level in mice (Furth's AK stock) during the preleukemic "normal" state and after the disease, spontaneous or transmitted, was manifest and (b) the level of 17-ketosteroid excretion by leukemic human subjects.

In AK mice the disease is associated with a definite increase in adrenal size in males (38% increase) but not in females (5% increase). In mice showing signs of leukemia, the concentration of adrenal cholesterol (both sexes combined) is much lower than during the preleukemic period (preleukemic 4.78%, leukemic 2.64%). Pituitary adrenocorticotrophic hormone, administered daily to several mice from the time of transmission of the

leukemic cells, did not affect the course of the disease. The adrenals were increased in size, but the adrenal cholesterol concentration was similar to that of untreated leukemic mice. Experiments to determine the effects of some adrenocortical steroids are now in progress.

Determination of 17-ketosteroid excretion of leukemic subjects yielded equivocal results, 3 men and 2 women excreted definitely subnormal quantities, while 2 men and 1 woman excreted amounts within the normal range.

These results do not prove the participation of the adrenal cortex in clinical or in experimental leukemia. They do, however, add further evidence indicating the possible relationship of adrenocortical function to lymphatic leukemia.

**Enhancement of subtilin activity by methylation.** J. C. LEWIS and EUGENE F. JANSEN (by invitation) *Western Regional Research Lab., Albany, Calif.* The bacteriostatic activity of subtilin for *Micrococcus conglomeratus*, *Staphylococcus aureus*, and *Streptococcus faecalis* was increased approximately 4, 2, and 5-fold, respectively, by treatment of the subtilin with dilute HCl in methanol. The greatest enhancement was found after 6 to 20 hours of incubation at room temperature of a 1% solution in 0.6 N HCl—90% methanol or after 20 to 40 hours in 0.03 N HCl absolute methanol. The activity decreased markedly on more prolonged or more drastic treatment. The isolated, enhanced-activity product contained 1.9%—OCH<sub>3</sub> by Zeisel as compared with a negligible test (0.1%) in the unmodified subtilin. The per cent OCH<sub>3</sub> obtained was the same with Zeisel reaction times of 30 minutes or 2 hours. The amino nitrogen (as determined by formal titration) was unchanged. The group or groups onto which methyl was introduced has not yet been determined.

Treatment of subtilin in methanol with diazo methane resulted in inactivation although methyl was introduced to the extent of 0.6% (calculated as OCH<sub>3</sub>). The amino nitrogen content of this product had been decreased one-third from the original subtilin.

**The isolation of metabolites of adrenal cortical hormones from human urine.** SEYMOUR LIEBERMAN (by invitation), KONRAD DOBRINER, C. P. RHOADS *Sloan-Kettering Inst for Cancer Research, Memorial Hospital, New York, N. Y.* Three substances which can be considered to be metabolic products of the adrenal cortical hormones have been isolated from neutral ketonic fractions of human urine which has been hydrolyzed by acid.

One, in common with many adrenal substances, possesses an 11-oxygen group. It is etiocholanol-3

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<sup>1</sup> Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

$\alpha$  dione-11,17,<sup>1</sup> m p 188-9°,  $[\alpha]_D^{25} = +95.8^\circ$ . It formed a monoacetate, m p 163-4°,  $[\alpha]_D^{25} = +115.4$ . It was identified by direct comparison with the synthetic sample prepared by Dr L Sarett.<sup>2</sup>

Because each of the other two substances has a double bond in ring C between C-9 and C-11, they probably are transformation products produced by dehydration during the acid hydrolysis of the urine from the corresponding 11  $\beta$  hydroxy compounds. Both were detected by means of their infrared absorption spectra. One of these substances is  $\Delta^9,11$ -etiocholanol 3 $\alpha$ -one-17, m p 169°,  $[\alpha]_D^{25} = +151$ , epoxide m p 182°,  $[\alpha]_D^{25} = +116.4$ . It was identified by comparison (m p, rotation and infra red spectrum) with a sample synthesized by Dr Sarett.<sup>3</sup> The second unsaturated compound,  $\Delta^9,11$  androsteneol 3 $\alpha$ -one-17, was isolated in the form of its epoxide, which melted at 196-8°,  $[\alpha]_D^{25} = +90.4$ . It formed a monobenzoate, m p 186-8°,  $[\alpha]_D^{25} = +85.4$ , and a monoacetate, m p 160-2°,  $[\alpha]_D^{25} = +82.7$ , and was oxidized to diketone epoxide, m p 213-5°,  $[\alpha]_D^{25} = +116$ , which was shown to be identical with 9,11 epoxy androstenedione-3,17.<sup>4</sup>

The relationships of the compounds to health and diseases and to steroid metabolism will be discussed.

**Apparent identity of antitrypsin of egg white and ovomucoid** HANS LINEWEAVER and C W MURRAY (by invitation) *Western Regional Research Laby,<sup>5</sup> Albany, California*. Recent interest in antitrypsins as antibiotics and as animal growth retarding factors stimulated this study of egg white antitrypsin, which has not been identified previously with any recognized protein component of egg white.

Antitrypsin was found in equal amounts in thin and thick white but is nearly absent from yolk. Antitryptic activity was found quantitatively in ovomucoid prepared without heat treatment. Attempts to fractionate it further were unsuccessful. A limited electrophoresis study failed to reveal other components in this fraction than ovomucoid. One molecule of ovomucoid (molecular weight, 29,000) caused about 50 per cent inhibition of one molecule of trypsin. Heat denatured ovomucoid has no antitryptic activity. These findings indicate that ovomucoid and antitrypsin are identical.

Denaturation of ovomucoid was indicated by two tests. (1) Native ovomucoid (active antitrypsin)

resisted hydrolysis by chymotrypsin, which it does not inhibit, whereas heat denatured ovomucoid, which possessed little or no antitryptic activity, was readily hydrolyzed by chymotrypsin, and (2) the nitroprusside test for S-S groups was about five times as strong for heated as for unheated ovomucoid. Both native and denatured ovomucoid are very soluble in water.

Partial analysis revealed the following percentage composition: Nitrogen, 12.0, amino nitrogen, 0.7, acetyl, 4.5 to 5.2, sulfur, 2.2, cystine, 6.1, histidine, 3.2, tyrosine, 5 to 6, tryptophane,  $\leq 0.3$ , carbohydrate, 26.4 (as glucose), optical rotation,  $-56^\circ$  ( $\alpha_D^{25}$ ), and SH (free or masked), none detectable.

**Enzymes of fresh infertile hen eggs** HANS LINEWEAVER, HERMAN J MORRIS (by invitation), LEO KLINE (by invitation) and R S BEAN (by invitation) *Western Regional Research Laby,<sup>1</sup> Albany, Calif*. Enzymes reported to be present in unincubated eggs were reinvestigated primarily because of their potential importance in dried egg deterioration.

Some enzymes have been erroneously reported to occur in fresh eggs due to use of faulty procedures. Thus repetition of Koga's procedure for detection of autolipolysis (lipase and lecithinase) invariably showed acidity increases were attributable to microbial activity. Although tributyrinase occurs in eggs, lipases capable of hydrolyzing higher lipids (the only ones present in eggs) were absent within experimental error. Oxidases were erroneously reported to be present in egg white. Color development of autooxidizable phenolic substrates added to raw and heated egg white were compared by Koga. Inhibition of autooxidation, apparently caused by the excess free SH groups of heated egg white, lead to the interpretation that the heat treatment had destroyed an enzyme. Negative oxidase results have been consistently obtained when correction was made for autooxidation.

Yolk enzymes, which generally appear in the livetin fraction, are capable of hydrolyzing tributyrin, triacetin, methylbutyrate, benzoylbutyrate, acetylcholine, benzoylcholine, acetyl  $\beta$  methylcholine, phenylphosphate, and starch. Eserine completely inhibits egg tributyrinase but neither liver nor pancreas tributyrinase.

Catalase was present largely in egg white. Peroxidase was not detected in either white or yolk.

The enzyme activities varied greatly from enzyme to enzyme but in no case did the specific rate correspond to more than 10 milliequivalents of substrate bonds split per kg egg per minute at 30°. The activities are so low that it appears extremely doubtful that egg enzymes are primary causes of egg deterioration.

<sup>1</sup> Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U S Department of Agriculture.

<sup>1</sup> Lieberman S and Dobriner K. *J Biol Chem* 166: 733, 1946.

<sup>2</sup> Sarett L M. *J Biol Chem* 162: 619, 1946.

<sup>3</sup> We wish to thank Dr Sarett for the synthesis of this compound.

<sup>4</sup> Lardon A and Reich H. *Helv Chim Acta* (in press).

<sup>5</sup> Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U S Department of Agriculture.

pholipids has been established. Isolation and identification of the inositol-containing phospholipid has been attempted. Treatment with ethanol of an ethereal solution of the acetone-insoluble lipids from the livers of over 2000 rats (available from previous studies in this Department) gave a crude phospholipid fraction containing about 3 per cent inositol.

Fractional precipitation studies with various combinations of organic solvents have been made and it has been found that methanol, ethanol and ethyl acetate precipitate phospholipid fractions with increased inositol content from chloroform solutions of the crude phospholipid. The solubility characteristics of the rat liver substance appear to differ, however, from those of the inositol-containing phospholipids of soya bean and brain described by Woolley and by Folch. Further, the substance from rat liver appears to be more resistant to acid hydrolysis than soya-bean lipositol. The results of fractionation studies and of examination of the products of hydrolysis will be presented.

**The relation of boron to certain plant oxidases**  
ROBERT MACVICAR (by invitation) and R. H. BURRIS, *Dept of Biochemistry, Univ of Wisconsin*. Although boron is unquestionably needed for normal growth and metabolism of higher plants, its specific function is unknown. The relation of boron and boron deficiency to the enzymatic oxidation of dihydroxyphenylalanine and other substrates capable of forming addition complexes with boric acid indicates that boron may affect the enzymatic oxidation of such compounds.

Homogenates and chloroplast suspensions from boron deficient soybean and tomato leaf tissue showed about double the rate of endogenous respiration given by preparations from leaves produced at normal boron levels. In deficient tissues the rate was often depressed when boric acid was added in final concentration of M/10-M/100. The lactic and glycolic acid oxidizing systems of leaf tissue showed no increase with boron deficiency, but the polyphenoloxidase activity using dihydroxyphenylalanine as a substrate was markedly enhanced.

Boric acid was found to inhibit the endogenous rate of respiration of a washed chloroplast suspension from normal tobacco leaves as follows: M/1000, no inhibition, M/100, 11%, M/10, 21%, M, 34%. Boric acid at levels of M/100 and M/1000 was found to have little effect on the rate of oxidation of lactic, glycolic, and ascorbic acid by cell-free extracts of tomato, tobacco, soybean, and cabbage. Ascorbic acid oxidation by cabbage showed only slight inhibition in the presence of molar borate, lactic and glycolic acids were affected to a greater degree. The oxidation of dihydroxyphenylalanine by soybean, however, was inhibited about 25% by M/100 boric acid. This inhibition occurred in

both normal and boron deficient plants, and to about the same degree in each. The inhibition produced by M/100 borate was completely reversed by M/10 mannitol.

**Serum precipitable iodines in recognition of cretinism and in control of thyroid medication**  
EVELYN B. MAN, CHARLES CULOTTA (by invitation), DOROTHY SIEGFRIED (by invitation), and CARTER STILSON (by invitation), *Biochemistry Lab of the Dept of Psychiatry, and Dept of Pediatrics, Yale Univ, School of Medicine*. It has been suggested that irrevocable damage occurs in children when clinical symptoms of cretinism becomes complete. Recognition of thyroid hypofunction before all symptoms develop would permit earlier thyroid medication. Because clinical cretinism is accompanied by distinct decreases in serum precipitable iodine, measurement of serum iodine in questions of cretinism might hasten diagnosis without reliance on clinical symptoms alone. Serum precipitable iodines of 8 untreated cretin children were all subnormal, below 2 gamma per cent, in contrast to iodines ranging from 3.7 to 7.9 of 66 non-cretin children. With the exception of one cachectic child low iodines occurred only in cretins.

Measurement of serum precipitable iodine is more reliable than evaluation of serum cholesterol in the diagnosis of cretinism. Iodines of 7 untreated children with clinical cretinism were all subnormal. Cholesterols of only 3 of these children were above 300 and of three were below 250 mg per cent.

Six cretin children have been followed after administration of desiccated thyroid. The serum precipitable iodine of the child with best clinical response, has risen to 4.3 gamma per cent, those of the two with persistent signs of thyroid hypofunction are only 1.6 and 2.4 gamma per cent. The 3 month baby with good clinical improvement was given  $\frac{1}{2}$  of a grain of thyroid daily and the 13 month baby with poor clinical response  $\frac{1}{2}$  a grain. Control of thyroid dosage to maintain a normal serum precipitable iodine might facilitate clinical improvement in children.

**Application of the saturation principle to liver function**  
M. F. MASON, G. HAWLEY (by invitation), W. LEWALLEN (by invitation) and H. G. MONTGOMERY (by invitation), *Parkland Hospital and Southwestern Medical College, Dallas, Texas*. Measurements of the maximum capacity of the livers of normal unanesthetized dogs to excrete bromsulfalein have been made as follows. After a suitable priming dose the dye is injected by constant intravenous infusion at a rate estimated to maintain a constant high plasma level. Urine is collected quantitatively over 10 to 20 minute periods and frequent blood samples are drawn to permit plotting the actual plasma concentration curve. The rate of bromsulfalein excretion by the

liver is calculated from the rate of infusion corrected for the small amount lost in the urine and any observed change in plasma concentration upon the confirmed assumption of an essentially extracellular distribution of the dye

Preliminary results indicate that a maximum of about 0.4 mg dye/kg body weight per minute may be disposed by dogs with plasma concentrations (3 to 6 mg %) which appear to establish saturation of the mechanisms excreting the dye

The findings of Wierzechowski and Fiszal (Biochem Zt 282 124 (1935) that the utilization of galactose is irregular during brief periods of infusion were confirmed. In addition galactose is utilized to a considerable extent extra hepatically, and hence is unsuitable for the saturation procedure described above

Experiments to establish the minimum saturation level for bromsulfalein, to relate the mass of dye disposed per unit time to mass of liver tissue, and experiments upon dogs with experimental liver impairment or insufficiency are in progress

The proteins of mammalian spermatozoa DENNIS T. MAYER and LLOYD E. THOMAS (introduced by A. G. Hogan) *Depts. of Agricultural Chemistry<sup>1</sup> and Biochemistry,<sup>2</sup> the Univ. of Missouri, cooperating* Neither boar nor ram spermatozoa contain nucleoproteins extractable by 1 M or 2 M sodium chloride. Spermatozoa from ejaculated semen were washed free of semen plasma and extracted with the sodium chloride solutions (1) without further treatment, (2) after extraction with alcohol and ether and subsequent drying and (3) after thorough grinding with powdered glass between closely fitting glass cones. Ordinary methods of grinding failed to rupture the spermatozoan heads

Extraction of the washed, intact spermatozoa with sodium hydroxide solutions and subsequent neutralization of the extract has yielded fractions as follows: (1) a small fraction precipitating at about pH 11, (2) a relatively large fraction precipitating at about pH 6, (3) a fraction precipitating at about pH 3. Further work is in progress on the purification and characterization of these fractions

Hepato-renal factors in circulatory homeostasis IX Properties of a partially purified hepatic vaso-depressor principle ABRAHAM MAZUR and EPHRAIM SHORR *Dept. of Medicine, Cornell Univ. Medical College and The New York Hospital, New York City* A vaso depressor principle (VDM), originating in liver and skeletal muscle as a consequence of low oxygen tensions, is regularly present in serum of animals during the irreversible stage of hemorrhagic and tourniquet

shock, and is produced by these tissues on anaerobic incubation *in vitro* (Shorr, Zweifach and Furchgott, *Science* 102 489, 1945). VDM is extractable from these tissues by physiological saline and assayed by the depression induced in the reactivity to epinephrine of the terminal arterioles and precapillary sphincters of the exteriorized rat meso appendix

A VDM preparation obtained by saline extraction of anaerobic beef liver has been partially purified and concentrated 8,000 times, on the basis of nitrogen content. With the most active preparations, a positive test is obtained by the intravenous administration of 0.3 gamma solids into 100-150 gram rats. It is non dialyzable and gives the characteristic protein tests. Activity is rapidly destroyed by crystalline pepsin and trypsin and by low concentrations of iodine. A partially purified VDM preparation contained 15.7% N, 0.1% P, 0.26% Fe and 0.5% reducing substances but no pentoses. On acid hydrolysis, analyses have established the presence of glutamic acid, phenylalanine, tyrosine, arginine and histidine. Histidine accounted for 21% of the total N, a value similar to and characteristic of globin from hemoglobin. Hemin is absent. Concentrated solutions have a light yellow color with no characteristic absorption maxima in the visible spectrum. Preliminary data are available as to the behaviour of VDM during electrophoresis and ultracentrifugation [Aided by grants from the Josiah Macy, Jr. Foundation and the Eli Lilly Co.]

On the mechanism of the anomalous action of iodine in lowering the basal metabolic rate J. F. McCLENDON and WM. C. FOSTER (by invitation) *Hahnemann Medical College, Philadelphia* Since we have shown that proteins can be iodinated under conditions compatible with life and that such proteins contain thyroxine, we have studied the iodination of proteins inside the pituitary gland of living sheep. One sheep was fed 100 mg potassium iodide per day for 66 days. At the end of this period its pituitary gland weighed 1.625 grams and contained 263 per cent as much protein bound iodine as the control. The control sheep was fed 3 grams of thiouracil (deracil) per day for 41 days in order to bind any traces of iodine that could not be eliminated from its food. Its pituitary weighed 1.18 grams. The sheep fed iodide had a pituitary containing a much greater relative and absolute amount of protein bound iodine. It is postulated that this protein-bound iodine acts like thyroid hormone in inhibiting the formation of thyrotropic hormone, and that the decrease in thyrotropic hormone leads to less activity of the thyroid and therefore lower basal metabolic rate. We have confirmed these results on other animals to be reported elsewhere. [We are indebted to the Lederle Labs for the deracil.]

<sup>1</sup> Missouri Agricultural Experiment Station

<sup>2</sup> School of Medicine University of Missouri

The effect of folic acid on the vitamin A stores of rats A B McCOORD (by invitation), B L GOFF (by invitation), C F LAVENDER (by invitation) and S W CLAUSEN *Dept of Pediatrics, Univ of Rochester School of Medicine and Dentistry, Rochester, New York* Two hundred and nineteen 9 to 10 weeks old rats, the vitamin A stores of which were uniform, were divided as fairly as possible in regard to size and sex into 8 groups Groups 1, 2, 3 and 4 were given a purified diet deficient in vitamin A and folic acid, but containing all other substances essential for normal nutrition Groups 5, 6, 7 and 8 received the same diet adjusted to contain 2 to 4% succinylsulfathiazole Groups 1, 3, 5 and 7 received 25 $\gamma$  to 2 mg of folic acid by injection or by mouth each day Groups 3, 4, 7 and 8 received 4000 International Units of provitamin A (carotene) by mouth every other day After the rats had received the diets 46 days, they were sacrificed

Male rats which received folic acid grew better than those which did not, growth was retarded by succinylsulfathiazole The males had a higher concentration of vitamin A in their plasma than the females The concentration of vitamin A in the plasma was distinctly higher in rats which received succinyl sulfathiazole, due perhaps to failure of deposition of the vitamin in the livers, liberation of the vitamin from its stores or a "protecting" effect of succinylsulfathiazole The rats in groups 1 and 5 showed better growth but had smaller vitamin A stores in their livers than the rats in the corresponding groups 2 and 6 In females, folic acid promoted the absorption of ingested carotene and its storage in the liver as vitamin A

Oxybiotin metabolism in the chick R H MCCOY, A E AXELROD, and K HOFMANN (introduced by H E Longenecker) *From the Dept of Chemistry, Univ of Pittsburgh, and Western Pennsylvania Hospital, Pittsburgh, Pennsylvania* Oxybiotin, the oxygen analog of biotin, can replace biotin in the nutrition of the chick This paper presents data concerning the mode of action of oxybiotin in the chick In a balance study it was found that there was little difference between the total biotin content of newly hatched chicks and that of chicks maintained for three weeks on a biotin low diet Since the total intake of biotin for three weeks was less than 0.85 $\gamma$  and about twice this amount appeared in the excreta, some bacterial synthesis must have occurred However, this quantity is insignificant in terms of the chicks' requirement for biotin Chicks which received a total of 32 $\gamma$  of oxybiotin intramuscularly retained about 45% of this activity in body tissues An additional 10% was recovered in the excreta

Tissues from chicks maintained for six weeks on

an egg-white diet contained the following amounts of biotin activity expressed as millimicrograms per gram of fresh tissue heart, 34, liver, 420, spleen, 23, and muscle, 12 In contrast, tissues from chicks given 10 $\gamma$  oxybiotin per day for five weeks by intramuscular injection contained heart, 220, liver, 2590, spleen, 120, and muscle, 185 m $\gamma$ /gram A large amount of this activity was retained in bound form since, for example, only about 5% of the total biological activity found in liver from injected chicks was liberated by autoclaving for two hours in aqueous suspension

Observations on the action of ascorbic acid in adrenal cortical function RALPH W MCKEE, THEODORE S COBBEY, JR (by invitation), and QUENTIN M GEIMAN (by invitation) *Depts of Biological Chemistry and of Comparative Pathology and Tropical Medicine, Harvard Medical School, Boston, Massachusetts* Ascorbic acid has been found necessary for the growth and multiplication of the malarial parasite, *Plasmodium knowlesi*, in monkeys (*Macaca mulatta*) (Proc Soc for Exp Biol and Med 63 313, 1946)

During the normal course of malarial infection with *P. knowlesi*, there are sharp decreases in liver glycogen and adrenal and blood ascorbic acid, with the production terminally of an acute state of stress These facts suggested the possibility of determining the mode of action of ascorbic acid by studying the interrelationship of adrenal hormones and ascorbic acid, with special emphasis on the liver glycogen

Adrenal cortical hormone extract (Parke-Davis, Eschatin) and 11-dehydrocorticosterone (kindly supplied by Merck & Co) were injected subcutaneously into 24 hour fasted normal and ascorbic acid deficient guinea pigs The normal animals gave a 5-fold increase of liver glycogen, while ascorbic acid deficient ones showed no increase Liver glycogen values for the vitamin deficient animals were not as low (0.23%) as the normal fasted pig values (0.09%) Determination of liver glycogen after intervals of fasting indicated that in vitamin C deficient animals there is a slower than normal decrease of liver glycogen, and no subsequent rise It appears, therefore, that ascorbic acid deficient guinea pigs have decreased rates of glycogenolysis and gluconeogenesis

An additional observation of considerable interest in the hormone treated normal guinea pigs was a 50 per cent drop of the adrenal ascorbic acid Hypophysectomy did not prevent this effect Adrenal cholesterol values are being determined and the study extended to include monkeys [Supported by a Grant-in aid to Harvard Univ from the United States Public Health Service]

Amino acids in the nutrition and metabolism of malarial parasites RALPH W MCKEE, QUENTIN M GEIMAN (by invitation), and THEODOR S



COBBLI, JR (by invitation) *Depts of Biological Chemistry and of Comparative Pathology and Tropical Medicine, Harvard Medical School, Boston, Massachusetts* Mouldcr and Evans (J Biol Chem 164 145, 1946) recently showed that chicken erythrocytes containing the malarial parasite, *Plasmodium gallinaceum*, are able to hydrolyze the host erythrocytes' protein. Thus it seemed desirable to determine whether or not malarial parasites form their own protein from that of the red cells.

Utilizing human erythrocytes parasitized with *P. knowlesi* and the plasma replacement cultural technique (J Exp Med 84 607, 1946), we found that d,l methionine (10 mg per cent) is the only amino acid required in the culture medium for growth and multiplication in 24 hours. It would appear, therefore, that the parasite must use some of the protein in the host cell to form its own protein. Whether the methionine is being utilized solely for the formation of parasite protein or for other biological processes as well, cannot be stated at the present time. In our cultures, methionine is not replaced by choline or by choline plus homocystine. The effects of analogs of methionine on growth and respiration are being evaluated.

In our study of the various essential and non-essential amino acids, using glucose as substrate, we found that d,l methionine stimulated the oxygen uptake of the parasitized erythrocytes by 30 per cent. The other amino acids have no significant stimulatory effect.

Moreover, it has been determined that the addition of 16 mg per cent of Stearn's amino acids to the culture medium enhanced *in vitro* growth and multiplication of the human malarial parasites, *P. vivax* and *P. falciparum* [Supported by a Grant-in-aid to Harvard Univ from the United States Public Health Service].

**Separation and properties of bovine whey proteins.** T. L. McMEEKIN, E. DELLAMONICA (by invitation) and J. H. CUSTER (by invitation) *Eastern Regional Research Lab., Philadelphia 18, Pa.* Electrophoretic analysis of bovine whey indicated the presence of at least four components in significant quantities. The relative proportion of each component varied with the stage of the lactating period. The variations were particularly striking at the beginning and end of lactation. The portion of whey insoluble in 2.0 M ammonium sulfate was found to be largely composed of material with a mobility (sq. cm. per volt per second) of  $2.4 \times 10^{-5}$  and  $4.3 \times 10^{-5}$  at a pH 8.3. On fractionation with ammonium sulfate, an electrophoretically homogeneous product with a mobility of  $2.4 \times 10^{-5}$  was obtained. The presence of a fraction with a mobility of  $1.8 \times 10^{-5}$ , characteristic of colostrum globulin, could not be detected in these fractions from normal milk.

The electrophoretic pattern of whey indicated that  $\beta$  lactoglobulin made up about 65% of the total protein of whey. Crystalline  $\beta$  lactoglobulin amounting to 80% of the total  $\beta$  lactoglobulin as indicated electrophoretically was isolated and found to be homogeneous at pH 7.0 to 8.4. However, this material was not homogeneous at pH 4.8 (Li, C. H., H. A. C. S. 68, 2716 (1946)). The  $\beta$ -lactoglobulin gave a solubility in water, after repeated crystallizations, of 0.16 mg N per ml at 30°C. Further crystalline material was obtained after the removal of  $\beta$  lactoglobulin by precipitating the filtrate with ammonium sulfate. After dialysis of this precipitate at 4.7 M ammonium sulfate was precipitated. On making the filtrate to pH 5.2 and removing salt, crystals were obtained. These crystals gave a higher solubility in water as well as in dilute salt solutions than did the main portion of  $\beta$  lactoglobulin. There was no difference in the mobility of these fractions at pH 8.4.

**The biuret reaction.** The measurement of the amount of copper bound JOHN W. MEHL, RICHARD J. WINZLER, and EVA PACOVSKA (by invitation) *Dept. of Biochemistry and Nutrition, Univ. of Southern California School of Medicine.* The amount of copper combined with the protein in the biuret reaction has been studied, using the general method applied by Borsook and Thumann<sup>1</sup> to a similar problem. Increasing amounts of copper added to alkaline solutions containing a fixed concentration of protein. Measurements of the light absorption were used in the calculation of the protein-copper complex, and polarographic measurements were used to determine the free copper.

The copper combined with protein has been expressed in terms of the number of grams of protein for each copper atom. Assuming that the complex involves the bonding of each copper atom to four peptide linkages,<sup>2</sup> the average residue weight of the protein may be calculated. The average residue weights obtained were 100 for bovine and human serum  $\beta$  globulin, 150 for bovine serum albumin, and 130 for human serum albumin.

A dissociation constant for the complex could also be calculated. Although errors in the original measurements are considerably magnified in the calculated values of the constant, no evidence of a consistent change with concentration was found with a ten fold change in copper concentration. Calculated as the product of the concentration of free copper and free protein divided by the concentration of combined copper (all expressed in gm. per 100 ml.), the dissociation constant ranged from  $1 \times 10^{-3}$  to  $4 \times 10^{-3}$ . Considering each four peptide bonds as one concentration unit of protein,

<sup>1</sup> Borsook H and Thumann K. V. J Biol Chem 98 671 (1933)

<sup>2</sup> Rosing M. B. and Yang P. S. J Biol Chem 99 755 (1933)

the dissociation constant in conventional units would be about  $2 \times 10^{-1}$

**The specificities of some dehydrogenases toward pyridine nucleotides** ALAN H MEHLER (by invitation), ARTHUR KORNBERG<sup>1</sup> (by invitation), SANTIAGO GRISOLIA (by invitation), and SEVERO OCHOA *Depts of Pharmacology and Chemistry, New York Univ College of Medicine Moulder, Vennesland, and Evans, (J Biol Chem, 160 305, 1945)* reported that malic, lactic, and isocitric dehydrogenases in pigeon tissue extracts use either diphosphopyridine nucleotide (DPN) or triphosphopyridine nucleotide (TPN) By spectrophotometric measurement of pyridine nucleotides at 340 mμ, we find that with oxaloacetate, pure malic dehydrogenase from pig heart (Straub, *Z Physiol Chem* 275 63, 1942) reacts about fifteen times more rapidly with DPN<sub>red</sub> than with TPN<sub>red</sub>, with pyruvate as substrate, the corresponding ratio of activities for crystalline lactic dehydrogenase is 100 1 The same reactions in pigeon liver preparations have similar ratios Isocitric dehydrogenase (pig heart and pigeon liver) reacts exclusively with TPN We confirm reports from Euler's laboratory that 1 (+) glutamic dehydrogenase, in liver extracts, reacts equally well with DPN or TPN

Moulder, *et al*, also described a dismutation between pyruvate and isocitrate, forming lactate, α-ketoglutarate and CO<sub>2</sub>, catalyzed by pigeon liver preparations with either DPN or TPN as coenzyme Since isocitric dehydrogenase was believed to require specifically TPN, we investigated this reaction further Pig heart extracts containing isocitric dehydrogenase and oxalosuccinic carboxylase, but little lactic dehydrogenase, catalyze this dismutation with TPN, but not with DPN, after crystalline lactic dehydrogenase (from beef heart, Straub, *Biochem J*, 34 483, 1940), is added Pigeon liver extracts also require TPN specifically to catalyze this reaction [*Supported grants from The Rockefeller Foundation, The American Philosophical Society, The Williams Watterman Fund, and the American Cancer Society*]

**The oxidative reaction of fermentation** OTTO MEYERHOF and PETER OESPER (by invitation) *Dept of Physiological Chemistry, School of Medicine, Univ of Pennsylvania, Philadelphia* If the oxidative reaction of fermentation is written

$$\text{d glyceraldehyde-3 phosphate} + \text{phosphate} + \text{DPN} \rightleftharpoons \text{d glyceral acid-1,3 diphosphate} + \text{DPNH} + \text{H}^+$$

the requirements of the law of mass action for this equilibrium have been shown to be fulfilled for

every component of the system over a range of about 500 1 The oxidizing enzyme of yeast, purified according to Warburg and Christian, served as catalyst Since the isolated system  $[\text{DPNH}] = [\text{glyceric acid-1,3 diphosphate}]$  the equation can be tested by keeping all components of the equilibrium constant except one In this case  $\log \frac{[\text{DPNH}]^2}{[\text{DPN}]} = \log \lambda + \log K$ , where  $\lambda$  is the variable component Log  $\lambda$  plotted against  $\log \frac{[\text{DPNH}]^2}{[\text{DPN}]}$  forms a straight line inclined at 45°, when  $\lambda$  is glyceraldehydophosphate, inorganic phosphate or  $\frac{1}{\text{H}^+}$  When all components are kept constant except coenzyme, the equation  $\frac{[\text{DPNH}]^2}{[\text{DPN}]} = K$  is likewise fulfilled

From these findings alone, it follows that a dissociable "diphosphoglyceraldehyde" cannot form in any large percentage, since this would alter the slope and straightness of the curves By combining this equilibrium with those of triose-phosphate isomerase and aldolase the conditions for detecting an addition product between phosphate and glyceraldehydophosphate are improved But even then the apparent  $K_{\text{isomerase}}$  for

$$\frac{\text{total glyceraldehyde ester}}{\text{dioxycetonephosphate}}$$

is only slightly increased For a very high concentration of phosphate (0.15 M) the apparent  $K_{\text{isom}}$  is increased from 0.042 to 0.057 on the average Although this may be taken as an indication for an excess formation of glyceraldehyde-ester due to some addition product, the reactivity, even at low concentrations of phosphate, becomes understandable only on the assumption that this product does not form except in the presence of the oxidizing system and in its enzymatic field of action

**The urinary vitamin excretion of young men during rehabilitation following semi-starvation** OLAF MICKELSEN and ANCEL KEYS *Laby of Physiological Hygiene, Univ of Minnesota, Minneapolis* Thirty-two men who lost 25% of their original weight during six months of semi-starvation were divided into four groups receiving 2630, 3030, 3430 and 3830 Cals per day respectively One-half of the men in each group received 1 mg thiamine and 1.5 mg riboflavin per day as pills whereas the others received placebos Three day urine samples were analyzed for thiamine, pyrimin and riboflavin after 6 and 12 weeks of rehabilitation The thiamine excretion was linearly related to the intake and the values for all groups conformed to the same straight line This line had a slope about

<sup>1</sup> Division of Physiology, National Institute of Health, U S Public Health Service

three times as steep as that for the excretion-intake relation in normal men, in other words, these previously starved men, who were laying down new tissue at a rapid rate, excreted in comparison with normals, about three times as much thiamine as would be expected from the intake. In contrast, the pyrimin excretion did not depart from the normal relation to intake, as a result, the proportion of thiamine to pyrimin in the urine was grossly abnormal.

The daily riboflavin excretion for the placebo groups receiving 1.9 to 3.6 mg. riboflavin per day was 0.07 to 0.25 mg., whereas that for the supplemented groups at intakes of 3.4 to 5.1 mg. was 0.90 to 1.36 mg. [*Sponsorship will be acknowledged in later publication*]

The excretion of 17-ketosteroids by normal young men ERMA V O MILLER, OLAF MICKELSEN and ANGEL KEYS *Laby of Physiological Hygiene, Univ. of Minnesota, Minneapolis*. The urinary excretion of total, neutral 17-ketosteroids by normal young men was studied by means of the Zimmermann colorimetric procedure applied to the extract from 2 ml. of urine. This gives the same results as the macro procedure and excellent recoveries of added androsterone.

Twelve sedentary men (ave. age = 28) on their regular diets excreted per 24 hrs.  $11.3 \pm 3.58$  mg. of 17-ketosteroids. Each individual seemed to have a characteristic level of excretion. Two to 5 samples secured from each of 12 subjects 7-81 days apart showed an average deviation of each man from individual mean 24 hr. excretion of 5.5% ( $\sigma = \pm 3.67$ ).

In a series of 55 samples from 12 men maintained on a constant regimen of diet and activity the average excretion of 17-ketosteroids during the day was  $0.47 \pm 0.098$  mg. per hr. while that at night was  $0.27 \pm 0.054$  mg.

In 4 young men, the hourly 17-ketosteroid excretion was followed during minimal physical activity. Three of the men showed considerable fluctuations in excretion during the day with an indication that peaks in the excretion curve followed the meals. The fourth showed very little change throughout the day. One subject essentially duplicated his excretion curve 4 weeks later. In none of these cases was there a simple uniform trend in the excretion curve throughout the day. [*Sponsorship for this work will be acknowledged in final publication*]

Changes in rat liver enzyme activity with inanition LEON L. MILLER (introduced by W. H. Pearlman) *Dept. of Biochemistry, The Jefferson Medical College, Philadelphia, Pa.* The activity of rat liver catalase, xanthine dehydrogenase, cathepsin and alkaline phosphatase has been measured by using homogenates of the livers from Sher-

man strain rats after complete starvation for 7 days.

When compared with well fed normal controls on a 25% casein diet adequate in vitamins, the livers of the fasted animals show a loss of catalase activity which parallels the loss of liver protein.

The xanthine dehydrogenase activity is even more markedly reduced so that the activity expressed in units per gram of liver protein of fasted rats is significantly lower than that of the normal livers. The difference is even greater when expressed in terms of units per hundred grams initial body weight.

Cathepsin activity per gram liver protein is maintained or increased with starvation, however, the activity per 100 grams initial body weight may decrease somewhat. The alkaline phosphatase activity behaves similarly.

The pigment, lipids and proteins of the malaria parasite (*P. knowlesi*) DEMPSE B. MORRISON and HAROLD A. JESKEY (by invitation) *Dept. of Chemistry, Univ. of Tennessee, Memphis*. Parasites, isolated from the erythrocytes of infected monkeys, were prepared free of hemoglobin and stroma, and were analyzed as isolated or after drying at 70°. The average composition of 5 preparations, expressed as per cent, was pigment 10.4, lipids 28.8, and protein 60.7. The pigment is known to be hematin. The protein is sparingly soluble in veronal buffer at pH 8.6, contains approximately 14 per cent nitrogen, and is separable into 3 components on electrophoresis in veronal buffer at pH 8.6. The extracted lipids, which contain some pigment, vary in color from light amber to dark brown, are solid at room temperature and are quite viscous at 37°. They contain from 16-32 per cent of non saponifiable material, cholesterol being the main component. The fatty acid fraction contains less than 0.3 per cent volatile acid, 36 per cent stearic acid, and 41 per cent of a liquid 18 carbon unsaturated acid (oleic?).

To study alterations in composition of the host cell resulting from parasite infection, suspensions of washed erythrocytes (0.9 per cent NaCl) have been analyzed. Five normal and 14 monkeys at varying stages and intensities of infection were used. All concentrations were calculated to unit concentration of 1 mM per 100 ml. of cell suspension. We find that as the parasite pigment increases and the hemoglobin decreases maximal changes in erythrocyte composition occur as follows: total nitrogen decreases by 44 per cent, total solids decrease by 35 per cent, the lipids increase by 550 per cent.

Changes in the electrophoretic pattern of the plasma proteins of monkeys (*Macaca mulatta*) with infections DEMPSE B. MORRISON, EDWARD H. BLOCK (by invitation), and HAROLD A. JESKEY (by invitation) *From the Dept. of Chemistry,*

*Univ of Tennessee, Memphis* Plasma proteins of 37 monkeys have been analyzed in the Tiselius-Longsworth apparatus. Eighteen of the monkeys were normal and served as controls, 19 were infected, 17 with *P. knowlesi*, and 2 with tuberculosis. Those with malaria survived from 4-13 days after parasites appeared in the blood. Plasmas were diluted with and dialyzed against veronal buffer (pH 8.6). When thus prepared and electrophoresed for 120-200 minutes, under optimal conditions plasmas of both normal and infected monkeys exhibited in both ascending and descending patterns 9 components exclusive of the beta anomaly. These components, in order of increasing mobility, were gamma, fibrinogen, X, 2 betas, 3 alphas, and albumen. In most patterns, however, the alpha<sub>1</sub> and X components were not separated from albumen and fibrinogen, respectively. Accordingly, the albumin and fibrinogen measurements include the alpha<sub>1</sub> and X components. Average changes in the electrophoretic components of the malarious plasmas, expressed as per cent of the average normal values, were albumen, -26.2, alphas, +115.0, betas, -16.8, fibrinogen, +71.4, gamma, -4.3. Except for the gamma component all changes were statistically significant. In the infections of longest duration the gamma globulin tended to rise above normal. The A/G ratios fell progressively with the duration of the infection, average values for the ratio being as follows: 4-day survival, 0.77, 5-day survival, 0.61, 6-day survival, 0.53, 7-day or longer, 0.40. The average A/G ratio for the normals was 1.03. Tubercular plasmas exhibited essentially the same patterns as observed in the longest surviving malarious group except for an increase in beta globulins.

**On the determination of fibrinogen** PETER R. MORRISON (introduced by John T. Edsall) *Dept of Physical Chemistry, Harvard Medical School*. Fibrinogen is the plasma protein which forms fibrin under the action of thrombin, and its determination must be based on this defining character. However, the yield of this reaction is subject to negative errors due to incomplete precipitation of fibrin, and positive errors due to occlusion of other plasma components. Conditions under which the amount of clot formed represents actual fibrinogen can only be determined using purified reactants.

Using fibrinogen and thrombin fractionated from human plasma by ethanol precipitation, complete yields were obtained at pH 6.3 at fibrinogen concentrations from 0.5 to 2.0 grams/l, and thrombin concentrations from 0.05 to 0.20 units/cc. Reduced yields were obtained at both higher and lower concentrations of the reactants.

Other proteins were occluded in proportion to their concentration but varying widely with their nature. Occlusion of serum albumin or  $\gamma$  globulin

was negligible, but 10-25% of certain plasma lipoproteins were occluded and could increase the clot weight by as much as 150%.

Study of the effect of fibrinogen and thrombin concentration and pH on occlusion revealed that conditions tending to minimize occlusion also favor formation of coarse structured clots which are opaque and synerize strongly. Since proteins of high molecular weight were occluded while smaller ones were not, physical entrapping in the clot appears important although other properties may also play a part.

Optimal conditions for obtaining complete yields together with minimal occlusion appear to be fibrinogen, 1 gram/l, thrombin, 0.05 unit/cc, pH, 6.10-6.20, clotting time 10-20 hours. When occlusion occurs its magnitude may be estimated and corrections made.

**Hemostatic properties of hemolytic agents** M. E. MUHRER (by invitation) and A. G. HOGAN *Dept of Agricultural Chemistry, Univ of Missouri*. When hemolyzed red cells were injected intravenously into hemophilia-like swine there was an immediate sharp drop in the coagulation time. The effects, however, were so large, sudden, and transient, that it seemed desirable to devise a means that would break the blood cells down slowly and continuously in the circulation. This was attained by the use of hemolytic agents. Acetyl phenylhydrazine, a hemolytic agent, improved hemostasis when injected subcutaneously. Thiodiphenylamine and *n*-dipropyl-disulfide, both hemolytic agents, were mildly effective hemostatic agents when administered orally. The feeding of onions had a similar effect. Saponin and sodium oleate produced a temporary sharp drop in the coagulation time when injected intravenously. This initial reduction, however, was followed by a negative phase in which the coagulation time was longer than before injection. The intravenous injection of hemolyzed red cells or a hemolytic agent such as saponin caused a sharp decrease in fibrinogen, cell volume, and prothrombin along with the immediate decrease in coagulation time. Saponin injections stimulated an increased production of fibrinogen after the immediate initial drop and eliminated the possibility that the refractory coagulation phase was due to afibrinogenemia. The refractory phase of the coagulation time was accompanied by a further decrease in prothrombin and it was postulated that the prolonged coagulation time was due to hypoprothrombinemia.

**Isolation of alpha-mono-palmitin from pancreas** PAUL L. MUNSON (by invitation), MARY ELLEN JONES (by invitation), ARTHUR E. HEATH (by invitation), and F. C. KOCH *Biochemical Research Dept., Armour Labs., Chicago*. Hog pancreas was ground and extracted with 60 per cent alcohol. The aqueous alcohol extract was concen-

trated to small volume under diminished pressure, and after removal of separated fat, extracted with petroleum ether. Pearly white crystals of alpha-mono palmitin separated in the petroleum ether layer, and were essentially pure after one crystallization from  $\text{CCl}_4$ .

Saponification with alcoholic base yielded essentially pure palmitic acid, characterized by melting point, mixed melting point, and neutralization equivalent, and glycerol, identified by acrolein formation, specific gravity, refractive index, boiling point, acetyl number, and formation of the tri-benzoate. The isolated alpha monopalmitin was differentiated from beta mono palmitin by reaction with periodic acid and melting point, and further identified by saponification equivalent, acetyl number, and preparation of the di-benzoate.

The yield was 0.2 to 0.5 per cent of the weight of the fresh pancreas. The relative magnitude of the yield of alpha mono palmitin on application of this procedure to other animal tissues is under investigation. The significance of the possibly unique high content in the pancreas remains undetermined.

The gastric proteinase of yellow fin tuna (*Neothunnus macropterus*) EARL R. NORRIS and JAMES C. MATHIES (by invitation) *Dept. of Biochemistry, School of Medicine, Univ. of Washington, Seattle 5*. Previous work in this laboratory has shown that fish "pepsins" are markedly different from those of warm blooded animals. Yellow fin tuna "pepsin" was crystallized as needles by a modification of procedures previously used for the crystallization of pepsins. The activity of the purified preparation as measured by the Anson and Mirsky method with denatured hemoglobin is 0.56 pepsin units per mgr. of protein nitrogen at pH 1.6, which is approximately twice that of swine pepsin. This enzyme was found to be less soluble than pepsins previously worked with and lower concentrations of ammonium sulfate were used in salting out the enzyme. The minimum solubility was found to be at pH 3.0. The pH of greatest activity is 2.5 to 2.6. The enzyme is quite stable over the pH range 2.4 to 5.3 in dilute solution and is rapidly inactivated in alkaline solution. Other properties of the enzyme are reported.

Changes in nucleoprotein concentration in regenerating liver ALEX B. NOVIKOFF (by invitation) and VAN R. POTTER *McArdle Memorial Lab., The Univ. of Wisconsin*. Ribonucleic acid (PNA) and deoxyribonucleic acid (DNA) concentrations were determined at varying intervals following partial hepatectomy, from 13 hours to 23 days. The rate of liver growth during this period was calculated on the basis of % weight of the original liver restored.

The highest concentrations of PNA were found during the time of rapid growth ( $1\frac{1}{2}$ -4 days after

partial hepatectomy). The increased PNA concentration in the growing liver was expressed in terms of PNA concentration in the original liver, on a dry weight basis. The maximum increase obtained in any animal was 62%. Plotting % increase in PNA against time revealed the rate of increase to be most rapid between  $1\frac{1}{2}$  and 3 days. This was also the period of most rapid liver growth.

No consistent correlation was found between the rate of growth and changes in DNA concentration.

Several rapidly growing livers with high increases in PNA ( $1\frac{1}{2}$ -3 days) and several slowly growing ones with little or no increase in PNA ( $\frac{1}{2}$ - $1\frac{1}{2}$  and 5-19 days) were also analyzed for the following compounds: adenosine triphosphate, adenosine diphosphate, adenylic acid, free pentose-phosphate, lactic acid and glycogen. Except for the very low concentration of glycogen in the animals  $\frac{1}{2}$  day after partial hepatectomy, the concentration of these substances varied no more among these animals than among controls.

Response of penicillin-resistant strains of *Staphylococcus aureus* to extract of beef brain. LEO G. NUTINI and SR. EVA MARIA LYNCH (introduced by Fred W. Oberst) *From the Dept. of Experimental Medicine, Inst. Div. Thomae, Cincinnati*. In one experiment (I) subcutaneous infections were established in a series of 18 mice for each of 24 strains of *Staphylococcus aureus* proven resistant to penicillin in various laboratories, 6 were untreated, 6 received 1,000 O.U. sodium salts of penicillin, subcutaneously, daily, and 6 received 50 mg. brain extract soluble in 80 per cent alcohol, subcutaneously, daily. In another experiment (II) 25 strains were used, one dose of either penicillin or brain extract was given 2 to 6 hours prior to inoculation, and treatment was continued. The results of the two groups are as follows:

	I Therapeutic series		II Prophylactic series	
	Mortality (per cent)	Healing time (days)	Mortality (per cent)	Healing time (days)
Controls	84		50	
Penicillin treated	95	22	78	20
Brain extract treated	14	7	0.6	11

The results indicate the effectiveness of brain extract.

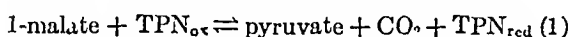
To determine whether the organism would develop resistance to brain extract, mice were inoculated with either a 12-hour, a 15 day, or a 30-day culture (3 day transfers) of each of the 25 different strains in media containing either 5.71

O U penicillin per ml or 0.5 per cent brain extract. The mortality is as follows

	12 hour	15 day	30-day
Total mice	450	390	360
Control	85%	55%	60%
Cultures with penicillin	94%	89%	100%
Cultures with brain extract	2.6%	3.8%	0%

All lesions in the penicillin series were purulent. Only one lesion developed in the brain extract series, and it contained pus for 2 days. There is no indication that the organisms develop resistance to brain extract.

**Reversible oxidative decarboxylation of malic acid.** SEVERO OCHOA, ALAN H. MEHLER (by invitation), and ARTHUR KORNBERG<sup>1</sup> (by invitation). *Depts of Pharmacology and Chemistry, New York Univ. College of Medicine.* The mechanism of CO<sub>2</sub> fixation in pigeon liver extracts has remained rather obscure. We have now obtained from pigeon liver an enzyme preparation that, in the presence of Mn<sup>++</sup>, catalyzes the reversible reaction



Reaction (1) is followed spectrophotometrically at 340 mμ.

The new enzyme has been purified 30–40 fold by fractionation with alcohol at low temperature and fractional adsorption on alumina gel. It is specific for triphosphopyridine nucleotide (TPN). There is no reaction with diphosphopyridine nucleotide (DPN), fumarate, or phosphopyruvate. Neither orthophosphate nor adenosine triphosphate participates in this reaction.

Reversibility of reaction (1) is demonstrated by the fact that in the presence of the enzyme, TPN<sub>red</sub> is rapidly oxidized on addition of pyruvate and NaHCO<sub>3</sub> saturated with CO<sub>2</sub>. Moreover, l-malate is formed through the TPN-linked dismutation: pyruvate + CO<sub>2</sub> + glucose-6-phosphate = l-malate + 6-phosphogluconate when the liver preparation is incubated with Mn<sup>++</sup>, pyruvate, CO<sub>2</sub>, glucose-6-phosphate, glucose phosphate dehydrogenase, and TPN.

Reaction (1) does not take place, whether in the presence of DPN or TPN, with a combination of pure malic dehydrogenase, purified oxaloacetic carboxylase (from *M. lysodeikticus*), and Mn<sup>++</sup>. [Supported by grants from the U. S. Public Health Service, The Rockefeller Foundation, The American Philosophical Society, and The American Cancer Society.]

**The effect of biotin deficiency on liver cholesterol storage in rats.** RUTH OKEY, SAMUEL LEFKOVSKY, and RICHARD PENCHARZ (by invitation).

From the Dept of Home Economics and the Division of Poultry Research, College of Agriculture, Univ of California, Berkeley, and the Dept of Pathology, Mt Zion Hospital, San Francisco. Biotin deficiency has been produced in rats placed at weaning on diets containing 36 per cent dried whole egg or 10.8 per cent dried egg white, with extracted casein, salts, sucrose and a crystalline vitamin mixture. Each diet furnished 2 mg of folic acid, 500 mg each of choline and inositol, and 10 grams cholesterol per kilogram.

Food intakes remained normal, even after biotin deficiency was well established.

Liver cholesterol values in animals fed these cholesterol-rich but biotin-poor diets were in the ranges previously noted for cholesterol-low diets containing raw casein, starch and yeast. Adding biotin to the egg diets produced marked liver cholesterol storage as well as clearing up of the deficiency symptoms. Rats placed at weaning on a cholesterol diet in which highly extracted casein was substituted for the egg white showed little liver cholesterol storage. Addition of biotin gave an average liver cholesterol value of 3.5 per cent in 9 weeks, as contrasted with 0.39 per cent for the animals on the egg white cholesterol diet. Another series of rats fed the extracted casein-cholesterol diet with biotin by pipette had 2 per cent liver cholesterol after 4 weeks on diet. A group of these animals was transferred to the biotin low diet without cholesterol and within 48 days the liver cholesterol had decreased to 0.21 per cent. [Part of this work was supported by funds from the Quartermaster Food and Container Institute for the Armed Forces Committee on Food Research Contract W-11-009 Q M 70202.]

**Hyperglycemia following intravenous injection of insulin preparations.** NORMAN S. OLSEN (by invitation) and J. RAYMOND KLEIN. *Depts of Psychiatry and Biological Chemistry, Univ of Illinois College of Medicine, Illinois Neuro-psychiatric Inst., Chicago.* It has been reported that intravenous injection of an insulin preparation (Lilly) into rabbits was followed by a marked, initial hyperglycemia. In contrast, injection of another preparation (NOVO) did not produce hyperglycemia (Duve, Christian de, Glucose, Insuline, et Diabète, pp XXVII, 307, Masson et Cie, Paris, 1945). In the present investigation, carried out with cats, it was found that intravenous injection of commercially available preparations of crystalline zinc and amorphous insulin (Lilly, Sharp & Dohme, and Squibb) and crystalline zinc insulin not containing preservative (Lilly) was followed by an initial, transient hyperglycemia; in contrast, no hyperglycemia was noted after intramuscular injection. The increase in blood glucose following intravenous injection, was observed in animals under three experimental

<sup>1</sup> Division of Physiology, National Institute of Health, U. S. Public Health Service.

conditions—intact, paralyzed with dihydro  $\beta$ -erythroidine, and anesthetized with amytal. The increase in glucose was evident following administration of 0.1 unit insulin per kilogram body weight, and was marked (30 mg per 100 ml blood) following 2 units per kilogram. The maximum increment was at 5–10 minutes after injection, and the blood glucose returned to the control level about 20 minutes after injection, at which time hypoglycemia ensued. The hyperglycemic effect was found to be more pronounced in the anesthetized cats than in the others. In similar experiments with a "NOVO" insulin preparation (Terapeutisk Laboratorium A/S, Copenhagen, Denmark) no hyperglycemia occurred.

**Excretion of glycocholine by rats on low methionine, low choline diets.** ROBERT C. OLSON (by invitation), HOWARD A. EDER (by invitation), and FREDERICK J. STARE, *Dept. of Nutrition, Harvard School of Public Health, and Dept. of Biological Chemistry, Harvard Medical School, Boston*. The formation of creatine from glycocholine and methionine in the liver of the rat is well established. The possibility that this reaction would be retarded in animals fed diets deficient in labile methyl groups led us to study the excretion of glycocholine by rats fed low methionine, low choline diets.

Male albino rats weighing from 225–295 grams were divided into six groups of 3–6 rats and fed three levels of methionine with and without added choline for six weeks. The source of the methionine was alcohol extracted peanut meal and/or casein supplemented in each case with cystine to make the total sulphur content 0.19%. Diet 1, 2, and 3 contained 0.12%, 0.30%, and 0.54% methionine respectively. Diets 1C, 2C, and 3C contained the same amounts of methionine plus 0.3% choline chloride.

All animals grew from 11–25 grams per day. The mean daily excretion of glycocholine in milligrams per day per kilogram body weight for groups fed their respective diets were 1,  $24.5 \pm 0.6$ , 1C,  $12.2 \pm 0.1$ , 2,  $11.6 \pm 1.1$ , 2C,  $7.9 \pm 0.5$ , 3,  $5.0 \pm 0.2$ , 3C,  $4.9 \pm 0.1$ . In contrast to the excretion of glycocholine, the excretion of creatine and creatinine was relatively unaffected. On the basis of methyl equivalents, choline was much less effective than methionine in controlling the urinary level of glycocholine. These data suggest that in the absence of adequate dietary methionine, the methylation of glycocholine is impaired and as a consequence glycocholine appears in the urine in increased amounts.

Blood levels of certain constituents in normal adults before and after ingestion of rutin. EUGENIE PAPAGEORGIS and FOSTER ADAIR (introduced by Howard B. Lewis) *Emory Univ.* Rutin, the rhamnoglucoside of quercetin, is said to pos-

sess vitamin P activity and this may be associated with the physiological action of vitamin C. Since practically nothing is known as to how vitamin P strengthens capillary resistance, this study was undertaken to see if rutin has any grossly noticeable effect on the level of certain blood constituents which may be involved in membrane permeability.

Fifteen normal adults volunteered to go on a low ascorbic acid diet for four weeks. During the third and fourth week they took 100 mg of rutin by mouth daily. Rutin was then discontinued and for four more weeks the normal diet was supplemented daily with 100 mg of ascorbic acid. During the last two weeks of high ascorbic acid intake, rutin was again administered in 100 mg doses daily. At the end of each of the eight weeks blood was collected and analyzed, the plasma for ascorbic acid, and the serum for calcium, sodium, potassium and total cholesterol. (Potassium determinations were made on only nine of the subjects.)

The data failed to indicate that rutin has any detectable influence on the level in the serum of cholesterol, calcium, sodium or potassium. More extensive work may show some influence by rutin on the maintenance of plasma ascorbic acid.

**The metabolism of estrone in the dog.** W. H. PEARLMAN, PASCHKEIS, K. E., RAKOFF, A. E. (by invitation), CANTAROW, A., and WALKLING, A. A. (by invitation) *Jefferson Medical College, Philadelphia*. A total of 1.3 grams of estrone as the acetyl derivative was injected intramuscularly into three external bile fistula dogs. The bile, urine, and feces were subsequently collected and extracted in an attempt to determine the fate of the estrogen. The results thus far obtained are summarized.

(1) Of the estrogenic material recovered in the excreta, the major portion is in the bile, a smaller portion is in the urine and a small but significant portion is in the feces. (2) Almost all of the estrogenic material in the bile exists in a "free" form soluble in ether, the ratio of conjugated to free estrogen in the feces is also small but somewhat higher than in the bile, this ratio is appreciably increased in the urine, however. (3) Fractionation of the estrogenic material into (a) ketonic weakly acidic phenols, (b) non ketonic weakly acidic phenols, and (c) strongly acidic phenols indicates that fraction (a) ("estrone" fraction) accounts for only a minor portion of the total biological activity of the bile, fraction (c) possesses some biological activity, indicating the possible presence of estriol in bile, urine, and feces.

The results indicate that although massive doses of estrone are administered, most of the hormone undergoes metabolic transformation in the course of 48 hours. A major portion of the biological activity is nevertheless preserved, a considerable



amount of the estrogenic material being readily extractable from the bile without resort to hydrolysis or other drastic treatment. The foregoing considerations render the external bile-fistula dog an excellent experimental subject for studying the metabolism of estrone and perhaps other estrogens as well.

**Physical chemical properties of crystalline botulinus A toxin** FRANK W. PUTNAM (introduced by W. R. Tweedy) *Camp Detrick, Frederick, Md.* Crystalline botulinus A toxin, the most potent toxin known, contains  $220 \times 10^3$  mouse LD<sub>50</sub> per mg nitrogen. In nitrogen content (15.8%), in amino acid composition, in susceptibility to inactivation by heat and alkali, in solubility (akin to that of a globulin), and in physical chemical characteristics, the toxin is a typical protein, apparently devoid of a prosthetic group (Putnam, F. W., Lamanna, C., and Sharp, D. G., *J. Biol. Chem.* 165: 735 (1946)). Toxin prepared with and without chloroform shaking is homogeneous in electrophoresis, migrating with a mobility of 2.75 and  $2.69 \times 10^{-5}$  cm<sup>2</sup> volt<sup>-1</sup> sec<sup>-1</sup>, respectively, at pH 4.4. The toxin sediments with a single symmetrical boundary in the ultracentrifuge, with a value of  $S_{20} = 17.3$ . The diffusion constant, corrected to 20°, is  $1.87 \times 10^{-7}$  cm<sup>2</sup> sec<sup>-1</sup>. The molecular weight calculated from  $S_{20}$  and  $D_{20}$  is 900,000.

Analysis of the boundary spread in electrophoresis, diffusion, and sedimentation has been made. Satisfactory agreement of the diffusion constant at different time intervals and a good fit of the normalized diffusion curves with the ideal distribution curve have been realized, but the boundary spread in the ultracentrifuge is greater than that attributable to diffusion alone. Preliminary attempts to photograph the active toxin in the electron microscope with the aid of the gold shadow technique have been unsuccessful. Formaldehyde inactivation of the crystalline material yields a toxoid which is homogeneous in electrophoresis but has negligible toxicity [*Studies conducted at Duke Univ. Durham, N. C. with D. G. Sharp, and at Camp Detrick with C. Lamanna*].

**Quantitative studies on the coagulation defect in hemophilia** ARMAND J. QUICK, *Dept. of Biochemistry, Marquette Univ. School of Medicine, Milwaukee*. The serum obtained immediately after hemophilic blood has clotted contains much unchanged fibrinogen and practically as much prothrombin as the original blood. When incubated at 37°C, all of the fibrinogen is usually clotted in 1 hour, but no demonstrable decrease of prothrombin occurs. This indicates that only a very small and fixed amount of thrombin is formed. On adding increasing quantities of thromboplastin prepared from rabbit brain to hemophilic blood, the amount of prothrombin converted to thrombin is

proportional to the amount of thromboplastin supplied. This reaction appears to be stoichiometric and not enzymatic.

Platelets contain little thromboplastin as determined by the acceleration of the prothrombin time on the addition of a platelet extract. Normal plasma deprived of platelets by high centrifugation exhibits a defective conversion of prothrombin to thrombin, but on adding this plasma to hemophilic blood, it readily clots the latter and causes a marked activation of the prothrombin. When normal native plasma low in platelets is added to hemophilic plasma also depleted of platelets, little prothrombin is changed to thrombin. These findings suggest that the thromboplastin required for the activation of prothrombin occurs in the plasma in an inactive form. This substance is probably identical with Howell's plasma thromboplastin and with the anti-hemophilic globulin of Taylor and his associates. The platelets appear to furnish the agent which converts this inactive thromboplastin to the active form. Its action is enzymatic. Hemophilic platelets behave normally and apparently contain a normal quantity of the activator, but the plasma lacks the thromboplastin precursor.

**The occurrence of  $\alpha$ -phospho-ribo-trihydroxyglutaric acid in liver** S. RAPOPORT and ROBERT H. WAGNER (by invitation) *The Children's Hospital Research Foundation, Univ. of Cincinnati, Cincinnati*. A nitrogen-free compound, found to accompany the nucleotides in the fractionation of trichloroacetic acid extracts of the liver of several species, has been identified as the  $\alpha$ -phosphate ester of trihydroxyglutaric acid (*J. Biol. Chem.* in press). A comparison of the substance isolated from dog liver with samples of the three isomers of trihydroxyglutaric acid, establishes its constitution as the ribo-isomer.

The phosphate group is hydrolyzable with difficulty by acid, but easily by alkali. The substance is characterized by a reaction with mercuric-potassium-iodide and alkali, yielding a yellow color with an extinction maximum of 383 m $\mu$ . It occurs in liver and kidney in amounts of the order of 100-200 micro mols per 100 grams.

**The calcium binding property of the serum proteins** ARNOLD J. RAWSON (by invitation) and F. WILLIAM SUNDERMAN, *The William Pepper Lab. of Clinical Medicine, Univ. of Pennsylvania, Philadelphia 4*. After separating the serum proteins by means of methanol precipitation of the globulins it is possible to measure the calcium binding property of both the albumin and total globulins without resorting to the isolation and purification of these fractions. In normal sera the average value of calcium bound to albumin was found to be 0.95 (s.e. = 0.04) milligrams of calcium per gram of albumin, and that of calcium

bound to globulin, 0.74 ( $s.e. = 0.03$ ) milligrams of calcium per gram of globulin

The calcium binding property of the protein fractions was studied in sera obtained from patients suffering from multiple myeloma, lymphogranuloma venereum, and sarcoidosis. It was found that in the sera of nine out of ten patients studied the value of the calcium binding property of albumin was increased to as much as six times the normal. The evidence suggests that an altered form of albumin may appear in the albumin fraction in these diseased states. It was also observed in these conditions that the value of the calcium binding property of the total serum globulins varied from the normal, and appeared to be dependent upon the predominating type of globulin present.

The hypercalcemia present in two of the cases of multiple myeloma was due to an increased concentration of calcium bound to protein. This increase was dependent upon 2 factors: (a) the increased binding power of the serum albumin, and (b) the increased concentrations of total globulins, with approximately normal binding property.

**Basic and acid groups of serum proteins in disease.** JOHN G. REINHOLD and HARRISON F. FLIPPIN (by invitation) with the technical assistance of ELAINE CLAUSEN (by invitation). *Division of Biochemistry, the Labys, and the Medical Dept., Philadelphia General Hospital, Philadelphia.* Basic and acid groups of serum proteins have been measured in a number of disease states. Orange G and safranine were used for this purpose. The capacity of the protein to combine with these dyes was measured at pH 2.2 (orange G, basic groups) and pH 11.5 (safranine, acid groups). The method described by Fraenkel-Conrat and Cooper<sup>1</sup> was used.

The serum proteins of normal individuals and most patients combined with quantities of orange G that agreed fairly well with the expected uptake calculated from the dye combining capacity of normal human serum albumin and globulin preparations. Serum proteins of some patients showed excessive or deficient dye binding capacities. The amount of safranine combined with serum protein was less than the calculated uptake in all except a few individuals, while major deviations were more numerous and marked.

The possibility that other acidic and basic substances present were blocking the reactive groups of the protein was tested by dialyzing the serum against buffers at pH 2.2, 7.4, or 11.5. No change in dye uptake occurred.

The discrepancies exhibited by certain sera are at least in part explained by differences in dye uptake by the several globulin components of the serum proteins.

<sup>1</sup> Fraenkel-Conrat, H. and Cooper, M. J. *Biol. Chem.* 154: 239 (1944).

The use of the Shay rat in studying anti-ulcer substances. E. A. RISLEY (by invitation), W. B. RAYMOND (by invitation) and R. H. BARNES. *Dept. of Biochemistry, Medical Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* The Shay rat has been adapted for the assay of various anti-ulcer substances. The general technique involves ligation of the pylorus after a preliminary 48 hour starvation, intraperitoneal administration of the test substance at the time of operation and finally examination of the gastric mucosa for evidence of ulceration 16 hours after the operation. Numerous factors must be controlled rigidly in order to obtain consistent results, and of prime importance are the age and weight of the test animals. In the studies to be reported male albino rats 8 to 10 weeks of age and weighing 125 to 150 grams have been used.

Lyophilized dilute HCl extracts of the upper 6 feet of the small intestine of hogs have been found to decrease appreciably the degree of gastric ulceration as compared with control animals. Results with this type of extract have been variable and not all have shown activity even when administered at a maximum level of 200 mg. per rat. Rather extensive studies of these extracts administered orally prior to ligation of the pylorus have indicated a complete lack of activity.

Urogastrone prepared according to methods described by others has been found to be very active in reducing the degree of gastric ulceration. Certain preparations have shown marked activity at a level of 25 mg. per rat when administered intraperitoneally. Analysis of gastric contents at the termination of the studies (16 hours post-operative) in relation to the severity of ulceration will be discussed.

**Influence of dietary protein, methionine and cystine on vitamin C synthesis in the rat.** EUGENE ROBERTS and CHARLES J. SPIEGEL (introduced by Harold C. Hodge). *Dept. of Biochemistry and Pharmacology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, New York.* The greatly increased excretion of vitamin C produced in rats by certain organic compounds probably represents an accelerated synthesis of the vitamin.

Adequately supplemented isocaloric diets in which only the protein and carbohydrate levels were varied were fed to groups of 4 adult rats each. After a 7- to 12 day preliminary period, the stimulating agent, sodium phenobarbital or chlorotone, was administered by stomach tube or in the diet.

Increasing the level of casein from 0 to 5 to 18 per cent resulted in mean daily excretions of 1.74, 2.40, and 7.50 mg. per day per rat respectively for the 7 to 10th days after the first feeding of phenobarbital. A further increase to 55 per cent resulted in a somewhat lower excretion (6.43 mg.). Similar

results were obtained with arachin. Only cystine and methionine of the 10 essential amino acids tested showed a marked accelerating effect on vitamin C excretion when added to the 5% casein diet, increasing it to approximately the maximal levels attainable when either of the drugs was given. Methionine had no effect on vitamin C excretion when the stimulating agents were not given. The addition of methionine to a diet supporting maximal vitamin C excretion depressed the excretion significantly.

Although inanition for 3 days prior to the start of daily administration of phenobarbital and for 7 days thereafter greatly decreased the ability of the rat to produce vitamin C, there was still a highly significant increase over the excretion prior to the feeding of the drug.

**Fluorometric method for determination of the pyridine nucleotides in animal tissues.** JEAN E. ROBINSON (by invitation), NORA LEVITAS (by invitation), FRED ROSEN (by invitation) and W. A. PERLZWEIG, *Duke Univ. School of Medicine, Dept. of Biochemistry, Durham, N. C.* Suitable tissue extracts, preferably prepared in 2% solution of nicotinamide containing  $\text{Ce}(\text{SO}_4)_4$ , may be analyzed for the content of the pyridine nucleotides employing the acetone alkali fluorometric procedure previously described for blood (J. Biol. Chem. 167: 157, 1947). In a series of analyses carried out on the same extracts of rat tissues by the above method and the specific bioassay with *H. para influenzae*, the comparative results shown below were obtained. The figures as given are in micrograms of DPN per gram of fresh tissue.

	Liver 12 analyses		Kidney 11 analyses		Muscle 9 analyses	
	Acetone	H para	Acetone	H para	Acetone	H para
Range	647-1290	706-1322	394-1045	452-955	372-655	336-520
Mean	1006	1036	725	759	492	454
SD	227	189	228	168	76	54

[This work was aided by grants from the Nutrition Foundation, the John and Mary R. Markle Foundation and the U. S. Public Health Service.]

**Oxidation-reduction potentials of cytochrome c.** F. LEE RODKEY (by invitation) and ERIC G. BALL, *Dept. of Biological Chemistry, Harvard Medical School.* Oxidation-reduction potentials of the cytochrome c system were measured electrometrically between pH 0.4 and 10.0 at 30°C in an atmosphere of nitrogen. Oxidation with ferricyanide, reduction with reduced phthiocol, and the method of mixtures have yielded concordant results. Potentials were measured with gold plated platinum electrodes against a glass electrode as the reference half cell. pH values of the buffer solutions were determined with the hydrogen

electrode at 30°C. Potential determinations were carried out in  $1 \times 10^{-4}$  molar cytochrome c solutions to which a suitable dye was added to an equivalent concentration of 5-10 per cent of the cytochrome present. Titration curves obtained from these solutions generally followed the theoretical curves for a reversible system with  $n = 1$  between 20 and 80 per cent oxidation.

Between pH 1.75 and 7.70 the  $E_0'$  of the system is +0.2540 volt, the  $E_0'$  pH curve in this region having a 0.0 slope. Measurement of  $E_0'$  values between 7.70 and 10.0 show that the  $E_0'$  decreases 0.060 volt per unit increase in pH. Preliminary determinations in strong acid solutions have not been entirely conclusive. There is some indication that the  $E_0'$  pH curve has a slope of 0.120 volt per pH in the range pH 0.4 to 1.75. These data may be interpreted to indicate that ferricytochrome c has a dissociating group with an approximate pK of 7.70 and, if the data in the acid region are valid, one might assume that two hydrogen ions are dissociating simultaneously from ferrocytochrome c with pK values of 1.75.

**The metabolism of the mucosa of the small intestine.** OTTO ROSENTHAL, *Harrison Dept. of Surgical Research, Schools of Medicine, Univ. of Pennsylvania, Philadelphia.* Dickens and Weil-Malherbe<sup>1</sup> recently reported that the *in vitro* metabolism of mucosa of the small intestine of rat and mouse differed from that of colonic and gastric mucosa of various species<sup>2</sup> by the complete absence of a Pasteur effect. Believing to have eliminated the possibility of an artefact these authors assumed that this exceptional metabolic behavior existed also *in vivo*.

Since intestinal epithelium of rat and mouse is extremely fragile, the metabolism of the more stable duodenal mucosa of the rabbit was studied manometrically by means of Warburg's indirect method which had also been used by the previous investigators. The following metabolic rates (first hour, initial dry weight) were obtained:  $\text{QO}_2 = 9.6$  (7-12),  $\text{QO}_2^{\text{N}_2} = 0.1$  (0-0.5),  $\text{QO}_2^{\text{N}_2} = 7.7$  (6.5-10). Thus, while respiration and anaerobic glycolysis were as high as in duodenal mucosa of the rat, aerobic glycolysis was minimal.

Because of the limited accuracy of manometry in the case of low aerobic glycolysis lactic acid was also determined colorimetrically. The averages, converted into manometric terms, were  $\text{QO}_2 = 0.8$ ,  $\text{QO}_2^{\text{N}_2} = 7.6$ , i.e., the aerobic glycolysis was but 10.5% of the anaerobic glycolysis.

The results prove clearly that the Pasteur effect is operative in duodenal mucosa of the rabbit. Probably the exceptional behavior of murine mu-

<sup>1</sup> Tr. Dickens and H. Weil-Malherbe, *Biochem. J.* 35: 7, 1941.

<sup>2</sup> O. Rosenthal and A. Lasnitzki, *Biochem. Ztschr.* 196: 340, 1925.

cosa of the small intestine is a species peculiarity if not an artefact

The urinary excretion of B-vitamins by surgical patients during intravenous feeding SAUL H RUBIN (by invitation) and ELMER L SPRINGHAUS *Nutrition Labys and Medical Dept, Hoffmann La Roche, Inc, Nutley, N J* Thiamine, riboflavin, N<sup>1</sup> methylnicotinamide, folic acid and pantothenic acid have been determined in consecutive daily urines of patients who were nourished before and after intestinal surgery exclusively by intravenous administration of protein hydrolysate, glucose, NaCl and KCl As the sole source of vitamins in the regimen, the protein hydrolysate provided an average of 0.03, 0.00, 0.86, 0.0087 and 0.70 mg per day, respectively These low intakes were reflected in prompt decreases in the excretion of all the vitamins tested except folic acid

After operation, a marked increase usually occurred, within a day or two, in the excretion of N<sup>1</sup> methylnicotinamide, folic acid, pantothenic acid and riboflavin but not thiamine Analysis of the data shows that this postoperative increase can generally be correlated with changes in urinary volume and nitrogen Following this postoperative "rebound," excretion gradually decreased again

These data will be discussed in relation to prevailing views on intestinal synthesis of vitamins [We are indebted to Drs J E Howard and L E Duncan, Jr, Dept of Medicine, Johns Hopkins Univ for the urine samples from their patients]

Hematological and growth responses in dogs given liver extracts containing the anti-pernicious anemia factor W R RUEGAMER and NANCY TORBER (by invitation) and C A ELVEHJEN *Dept of Biochemistry, Univ of Wisconsin, Madison* Hundreds of weanling mongrel dogs have been raised successfully on a synthetic ration supplemented with thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, choline, biotin, and the fat soluble vitamins A and D When niacin is omitted, the blacktongue which develops, responds to single doses of niacin, but after several treatments the dog fails to show the usual recovery If no additional factors are added, the animal shows anorexia, loss of weight, diarrhea, develops a progressive macrocytic anemia and eventually dies Folic acid has some action in prolonging the eventual collapse of the animal, but has no beneficial hematological effect when given alone

Young dogs were fed niacin deficient rations containing 30, 24, or 19% casein, or the latter plus 1% succinylsulfathiazole When the animals failed to respond to niacin therapy, they were given daily intramuscular injections of 0.5 cc of a pernicious anemia liver extract (Sharp and Dohme, 15 U S P units/cc) The animals receiving 24 and 30% casein rations responded completely both in hemo-

globin and growth without the addition of folic acid Animals which were fed the 19% casein ration showed some response but required folic acid to give complete recovery The animals receiving 1% succinylsulfathiazole and the liver extract responded very poorly, but demonstrated a complete response when given either free or bound folic acid

Animals given a folic acid supplement failed to respond until given a potent liver extract In the presence of folic acid a highly purified pernicious anemia preparation (Reticulogen, Lilly) was effective at very low levels

The tryptophane-sparing action of nicotinic acid W D SALMON *Laby of Animal Nutrition, Alabama Polytechnic Inst, Auburn* The level of dietary tryptophane has been shown to affect the requirement of the rat for dietary nicotinic acid In further studies of this effect, the converse relationship was also found to exist

A basal diet low in nicotinic acid and containing 40% of corn grits together with tryptophane free hydrolysate equivalent to 12% of casein was used Growth of young rats was less than one-third the normal rate when 0.10% of dl-tryptophane was added but was approximately normal when 0.20% was added When 0.02% nicotinic acid was added, however, growth was normal on 0.10% of added dl tryptophane When no tryptophane was added to the diet, rats failed to grow, even when 0.20% of dietary nicotinic acid was supplied

Rats grew at the normal rate for 8 weeks on a diet containing 25% of casein and 40% of corn grits without the addition of nicotinic acid Decreasing the casein content of the diet to 15% or to 9% did not reduce the growth rate if dl tryptophane was added to maintain the original tryptophane content of the diet or if 0.02% of nicotinic acid was added

Evidence was obtained that free dl-tryptophane was more effective as a source of nicotinic acid than was a comparable level of tryptophane in the casein molecule

The tryptophane sparing action of nicotinic acid may have marked economic significance in practical nutrition

The metabolism of testosterone by the livers of different species of animals LEO T SAMUELS and MARY PORTNER (by invitation) *Dept of Biological Chemistry, Univ of Utah Medical School, Salt Lake City, Utah* The metabolism of testosterone by the minced liver tissue of different species of animals has been investigated by chemical techniques The hormone is metabolized by an oxidative enzyme system which is inhibited by cyanids and partially by malonate The products of metabolism have been found to differ in different species, although the rate of disappearance does not differ greatly In chicken livers an alco-

holic 17-ketosteroid is formed which shows no significant absorption in the ultraviolet region from 220-300 millimicrons. It has androgenic activity.

No such compounds could be found in the products of testosterone destruction by human, rat, mouse, or rabbit liver. This explains the greater oral activity: subcutaneous activity ratio of certain androgens in the chick when compared with the same ratio in rats. It leaves unanswered the source of androsterone formed when testosterone is injected into human beings. Metabolism of the hormone by other tissues is being investigated as well as the chemical character of the products formed by the different livers. [Aided by grants from the International Cancer Research Foundation and Ciba, Inc.]

**The absorption of blood from the peritoneal cavity of the dog.** GEORGE S. SAMUELSEN (by invitation), GRACE E. GRIFFIN (by invitation), EDWARD MONTWYLER and SAM SEIFTER, Dept. of Biochemistry, Long Island College of Medicine, Brooklyn. The absorption of blood from the peritoneal cavity of dogs proceeds quite rapidly and it has been observed (J. Exper. Med. 80: 77, 1944) that tagged erythrocytes placed into the peritoneal cavity can be detected in the circulation within a short period. Since a single non-fatal hemorrhage is followed by a prompt but gradual influx of fluid and plasma protein into the circulation, it was of interest to observe whether the peritoneal absorption of blood is sufficiently rapid to contribute measurably to the restoration of circulating fluid, plasma protein and erythrocytes. Consequently normal and protein-depleted dogs were

subjected, under sodium pentobarbital anesthesia, to a single uniform hemorrhage (25 per cent of measured blood volume). In certain animals the withdrawn blood was injected immediately into the peritoneal cavity. Observations were made before and 24 hours after hemorrhage, during which period neither food nor water was allowed. Changes of circulating volumes and amounts of circulating proteins were calculated from determinations of the plasma volume, hematocrit, hemoglobin and plasma protein concentrations. No striking differences between the injected and non-injected animals of either group were encountered during the period of observation. However, on the average, the injected animals exhibited a more complete restoration of the plasma volume and a higher percentage return of the circulating plasma protein. In the protein-depleted dogs there was some evidence of a greater return of circulating hemoglobin. The absorption of blood from the peritoneal cavity was unattended by a change in the urine total nitrogen excretion, during a six-day interval. [Aided by a grant from Wyeth Incorporated.]

**Further observations on the relationship of tryptophane and nicotinic acid metabolism in humans.** HERBERT P. SARETT and GRACE A. GOLDSMITH (by invitation), Nutrition Research Lab., Tulane Univ. School of Medicine, New Orleans, Louisiana. On diets providing 40 or 100 grams of protein per day, the daily ingestion of 5 grams of dl-tryptophane leads to an increased urinary excretion of about 10 mg of N<sup>1</sup>-methyl-nicotinamide and of 75 to 100 mg of l-tryptophane after 5 to 8 days. There are no apparent changes in the nicotinic acid excretion as measured microbiologically, and no increase in nicotinic acid values after acid hydrolysis of the urine.

The diets providing about 40 grams of protein per day contained either 250 grams of unenriched flour (Wheat) or 60 grams of this flour and 190 grams of degerminated corn meal and grits (Corn). These diets supplied 5.5 to 6.0 mg of nicotinic acid per day. The urinary l-tryptophane and N<sup>1</sup>-methyl-nicotinamide were lower when corn was substituted for the wheat.

For subjects on the wheat regimen the addition of indole 3-acetic acid at increasing levels of 25, 50 and 100 mg per day for successive 6-day periods had no marked effect on the excretion of the above metabolites.

The riboflavin, thiamine, 4-pyridoxic acid, nitrogen and creatinine excretion were also studied in the above experiments.

**The fate of ribose in nucleoside degradation.** F. SCHLENK and M. J. WALDVOGEL (by invitation), Univ. of Texas, M. D. Anderson Hospital for Cancer Research, Houston. We reported previously (Arch. Biochem. 9: 455, 1946) the discovery of an enzyme system which causes the splitting of ribose from purine nucleosides, stabilization of the resulting ribose-1-phosphate, and subsequent transformation of the carbohydrate into products which do not give the characteristic pentose color with the orcinol reagent (absorption maximum at 660 mμ). The color observed resembles that obtained from hexoses with orcinol. Fractionation of the enzymatic incubation mixture yielded hexose-6-monophosphate. Somewhat less than half of the calculated amount has been obtained from guanosine in our best experiments. The analytical data indicate the identity of the product with Robison Ester. By control experiments without substrate and by determination of carbohydrate it was ascertained that the hexose was not derived from glycogen or present as such in the enzyme mixture.

For the conversion of pentose into hexose two explanations seem possible: a direct extension of the five-carbon chain, or splitting of two pentoses into smaller units and recombination of two three-carbon compounds. Experiments are under way to elucidate the mechanism involved.

Observations concerning the assimilation of inorganic phosphate by bakers' yeast GERHARD SCHMIDT, LISELOTTE HECUT (by invitation) and S J THANNHAUSER *Tufts Medical School, Boston*

It was shown by Jeener and Brichet that the absorption of inorganic phosphate by bakers' yeast is very strongly enhanced when the cultivation of the yeast in phosphate containing media is preceded by a period of incubation in media devoid of phosphorus compounds. Wime and somewhat later Schmidt, Hecut and Thannhauser found that practically all of the phosphate absorbed by the yeast under these conditions appears in the yeast cells in the form of an inorganic metaphosphate (discovered in fresh yeast by MacFarlane in 1936). According to the results of freezing point and conductivity determinations, the metaphosphate of yeast is a complex polyphosphate. It is dialyzable, the acid contains 0.3 per cent of iron which, until now, could not be separated from the substance. The accumulated metaphosphate disappears very slowly when the cultivation is continued in deficient or in complete media. The inhibitory effect of fluoride described by Jeener and Brichet was observed with concentrations which did not influence fermentation or respiration.

Fresh yeast, cultivated in presence of ammonium sulfate and phosphate, rapidly assimilates phosphate at rates exceeding by far those of growth during an initial period of 3 hours. The acid soluble and insoluble P fractions increase in similar proportions. Considerable amounts of metaphosphate appear during the first two hours but disappear rapidly afterwards, in contrast to the behavior of metaphosphate in yeast treated according to the conditions of Jeener and Brichet.

**Metabolism of tryptophane by vitamin B<sub>6</sub> deficient rats and mice** B S SCHWEIGERT (by invitation) and P B PEARSON *Nutrition Laby, Agricultural Experiment Station and School of Agriculture, 1 & M College of Texas, College Station*. The effect of feeding tryptophane to vitamin B<sub>6</sub> supplemented and deficient albino rats and mice on the urinary excretion of nicotinic acid and N'-methylnicotinamide has been investigated. Weanling animals were fed purified diets with and without added pyridoxine. After 2-4 weeks, urine collections were made for each group when the basal diets were fed. In subsequent 3 day periods, 100 and 50 mg of *DL*-tryptophane were fed to rats and mice, respectively, in addition to the basal diets. In all cases the urinary excretion of nicotinic acid and N'-methylnicotinamide was determined.

Pyridoxine supplemented rats excreted 810-2190  $\mu$ g per day of N'-methyl nicotinamide when fed tryptophane while the deficient rats excreted only 180-435  $\mu$ g per day. When the basal diets were fed, the two groups excreted 95-185 and 45-

140  $\mu$ g per day of N'-methylnicotinamide respectively.

The excretion of nicotinic acid when tryptophane was fed to the pyridoxine supplemented animals ranged from 95-430  $\mu$ g per day and only 16-35  $\mu$ g for the deficient group. 23-50  $\mu$ g and 10-24  $\mu$ g of nicotinic acid were excreted by the two groups when the basal diets were fed.

The results obtained with the mouse were qualitatively similar to those observed with rats.

When tryptophane was injected, a definite increase in the excretion of N'-methylnicotinamide and nicotinic acid was observed, which indicates that the formation of nicotinic acid from tryptophane is largely from tissue synthesis.

A substance derived from bovine plasma which produces leucopenia and lowers blood pressure. WAITER H SEEGER, ROBERT C MURPHY (by invitation), ARNOLD G WARE (by invitation), STEPHEN R BODNAR (by invitation) and M MASON GUEST *Dept of Physiology, Wayne Univ College of Medicine, Detroit, Michigan*. Intravenous administration of a heat stable protein, derived from bovine plasma, lowers blood pressure in the dog and guinea pig, and causes a temporary but profound leucopenia in the dog. The initial blood pressure depression is usually of short duration, but after recovery to, or near to, the pre injection level, a secondary fall frequently ensues.

The white cell count in blood from the femoral artery and vein decreases within 2 to 3 minutes following the administration of the substance to an average of 1/15 of the initial value. The differential pattern reveals a marked reduction in segmented forms and a relative increase in lymphocytes. The leucopenia lasts for 2 to 5 hours. The differential pattern then returns to normal. Normoblasts frequently are numerous during the recovery period. Leucocytosis following recovery is mild or entirely absent. Sedimentation rates and hematocrit readings are not altered significantly. This protein substance either *in vitro* or *in vivo* does not appear to alter the clotting mechanism in any way.

The purified protein fraction producing these effects contains tyrosine, is not dialyzable, is stable at temperatures up to 90°C for 2 to 3 minutes and is soluble in 0.9% NaCl, but not in distilled water. [Aided by a grant from the National Inst of Health Plasma and funds for a graduate Research Fellow were supplied by Parke, Davis & Co.]

**Chemical studies on blood and muscle from rabbits and rats paralyzed by dithiobiuret** SAM SEIFTER, DAVID M HARNES (by invitation), EDWARD MUNTWILER and JOSEPH SEIFTER *Dept of Biochemistry, Long Island College of Medicine, Brooklyn and the Wyeth Inst of Applied Bio-*

chemistry, Philadelphia Astwood and coworkers (Science 102 196, 1945) have reported that a reversible paralysis can be induced in rats by administration of dithiobiuret (DTB) in the drinking water. This observation stimulated an investigation of possible changes of the chemical composition of the blood and skeletal muscle of rabbits and rats exhibiting such paralysis.

Rabbits given daily doses of DTB (kindly supplied by the American Cyanamid Company) subcutaneously (7 mg per kilo body weight) and rats receiving the drug ad libitum in the drinking water (0.002 per cent as employed by Astwood, et al.) were found to develop paralysis of the fore and/or hind quarters. Usually the animals died after receiving the drug for from 5 to 8 days. When the paralysis had reached a severe degree the animals were anesthetized with sodium pentobarbital and arterial blood (drawn under oil by cardiac puncture) and skeletal muscle were obtained. The chemical analyses of skeletal muscle from animals with paralysis for water, chloride, potassium, sodium, total and acid soluble phosphorus, and creatine revealed no significant changes when compared with suitable controls.

Because of the relationship of DTB to guanidine compounds the blood sugar level was determined. When the paralysis became severe the animals, particularly the rabbits, exhibited a moderate hyperglycemia. The significance of the administration of DTB on carbohydrate metabolism as revealed by changes in the intravenous insulin and the intravenous glucose tolerance tests in rabbits has been studied.

Lipotropic factors in the treatment of cirrhosis in rats. E. J. Best, M. D. (Dept. of Medical Research, Univ. of Toronto, Can.) Cirrhosis was induced immediately into white rats of the Wistar strain by (a) administration of  $\text{CCl}_4$  vapour and (b) by ether hemorrhage, during liquid diet. When a moderate amount of water was allowed the animals died. Volumes and amounts of urine and the curative effects were calculated from determinations of choline, inositol and various vitamins. Hematocrit, hemoglobin, and albumin concentrations were studied. No regeneration of liver cells in the injected and control group were encountered. Choline and inositol precursors. Choline and inositol precursors were studied in concentrations. However, given in three times the dose, animals exhibited a permitted regeneration of the plasma volume and disappearance of fat, and a return of the circulating in fibrous tissue. A diet depleted dogs there the same effect as choline. No return of circulation had no favourable effect. A diet of blood from the damages but appeared attended by a change in

Relative gastro-intestinal excretion, during a six-day and vitamin A and the effect of xanthophyll. W. C. Salmon

(Laby of Animal Nutrition, Alabama Polytechnic Inst., Auburn, Alabama) When vitamin A-deficient rats were fed a vitamin E deficient diet with 0.2 ml of fresh lard per day, daily supplementation with 1 microgram of vitamin A alcohol did not prevent rapid loss in weight and death in 100 per cent of the animals. Vitamin A acetate prevented the rapid loss in weight and less than 40 per cent of the animals died. Beta-carotene, fed on a comparable International Unit basis (2 micrograms per day) produced appreciable growth and reduced the mortality to below 10 per cent. Addition of alpha-tocopherol produced good growth and greatly reduced the differences in response between carotene and vitamin A.

Xanthophyll (lutein) produced beneficial effects upon growth and reduced the mortality rate when added to vitamin A alcohol, vitamin A acetate and beta-carotene. Xanthophyll was destroyed as rapidly as carotene when aerated *in vitro* at 60°C in lard solution and both carotene and xanthophyll caused a marked acceleration in the rate of peroxide formation in the lard. This apparent vitamin A activity of xanthophyll may be explained on the basis that, in the absence of intestinal antioxidants, xanthophyll, like vitamin A and its precursors, is destroyed in the gastrointestinal tract, thus causing a corresponding amount of vitamin excretion, which is then able to accomplish its physiological function.

Metabolism of ribose in nucleic acid diet containing SCHLENK and M. J. WALDOGE (Univ. of Texas, M. D. Anderson Cancer Research, Houston) We re (Edgar G. Miller) (Arch. Biochem. 9 455, 1946) the Research and the enzyme system which causes, N. J. Adult dogs ribose from purine nucleosides, i.e., a diet containing the resulting ribose-1-phosphate, amino acids. On transformation of the carbohydrate, the daily calorie which do not give the characteristics per kg and the with the orcinol reagent (absorption, 40 fed dogs 660 mu). The color observed resembled, 40 days, the obtained from hexoses with orcinol. In oral to intracellular of the enzymatic incubation mixture for an additional hexose-6-monophosphate. Somewhat depleted dogs, there of the calculated amount has been, weight and nitroguanosine in our best experiments. Though intravenous data indicate the identity of the amino acids in the Robison Ester. By control experiments maintained just as substrate and by determination. During the period of it was ascertained that the hexose protein concentrations of from glycogen or present as sugar, acid fed dogs increased mixture.

For the conversion of pentose to hexose, the amino acids a slight explanation seems possible. A direct conversion of the five carbon chain, or splitting of the amino acids in into smaller units and recombination of the carbon compounds. Experiments are being conducted to elucidate the mechanism involved in plasma fibrinolysis.



gen, creatine creatinine, free and total cholesterol,  $\text{CO}_2$  capacity, blood sugar and urea N, serum phosphatase, total liver fat and liver glycogen. On a body weight basis the amino acid fed dogs had 11.6% more liver protein than those which received casein, the depleted dogs has 21% less.

The inhibition of conjugase by a polypeptide of *p*-aminobenzoic acid. EDITH S. SIMS (by invitation) and JOHN R. TOTTER, Dept. of Biochemistry, School of Medicine, Univ. of Arkansas, Little Rock. The effect of the yeast glutamic acid polypeptide of *p*-aminobenzoic acid on rat liver and chicken pancreas conjugases was determined. Identical results were obtained when either yeast extract or pteroyl hexaglutamylglutamic acid was used as substrate. The liberated pteroyl glutamic acid was determined with *Streptococcus faecalis* as the test organism. In initial experiments, with an incubation period of one hour, at pH 7, and substrate concentrations of 1.0 and 10  $\mu\text{gm}$  per ml, 1.25  $\mu\text{gm}$  per ml of the polypeptide produced 75 and 50% inhibition respectively, with both enzyme preparations. With other preparations of conjugases made by essentially the same procedures, 50% inhibition under similar conditions required as much as 12.5  $\mu\text{gm}$  per ml of polypeptide. In some cases there was no inhibition by the polypeptide at any concentration tried. When inhibition was observed it appeared to be competitive in nature, as indicated by an increased velocity of the liberation of PGA at increased substrate concentrations in the presence of the inhibitor. [Aided by a grant from the Williams-Materman fund of the Research Corporation. The *p*-aminobenzoyl polypeptide was furnished by Dr. S. Ratner, who suggested the inhibition studies. Dr. J. J. Piffner of Parke, Davis and Co. furnished the pteroyl-hexaglutamylglutamic acid.]

The composition of serum phospholipids. R. G. SINCLAIR, Queen's Univ., Kingston, Canada. There exists at present a serious discrepancy in the published evidence concerning the composition of the phospholipids in plasma or serum. Some data indicate that only lecithin and sphingomyelin are present in human plasma, other data indicate that cephalin makes up 20 to 40 per cent of the total phospholipid. Further study of the question seemed desirable.

The acetone insoluble fraction of the lipids extracted from the sera of various animals was isolated and analyzed for nitrogen, phosphorus, and choline. Aliquots were dialyzed and again analyzed. The methods used gave close to theoretical values for pure egg lecithin (N, 1.52, P, 3.92, C, 17.85, N/P, 1.026, C/P, 1.011).

Our data confirm other evidence of the gross contamination of serum phospholipids as prepared from the chloroform and petroleum ether solutions of the total lipids by precipitation with acetone.

The C/P ratios of the phospholipids from human sera and from beef serum were 0.99–1.00. However, those from two lots of turkey sera, after dialysis, had N/P ratios of 0.99 and 1.02 and C/P ratios of 0.75 and 0.78. Thus it appears that the sera of some animals contain cephalin while those of others do not.

On the mechanism of enzyme inhibition by sulfhydryl reagents. THOMAS P. SINGER (introduced by H. G. Wood), Division of Agricultural Biochemistry, Univ. of Minnesota and Dept. of Biochemistry, Western Reserve Univ. School of Medicine. Much attention has been focused recently on the inhibition of enzymes by reagents capable of specifically reacting with the  $-\text{SH}$  group. This has been taken as evidence that thiol groups are directly involved in the activity of such enzymes or that they might be actually located at the "active center." If this were true, then the inhibition of an enzyme by any specific  $-\text{SH}$  reagent should be about the same, regardless of the substrate used for assay. This question was tested experimentally by the use of amino acid oxidase and wheat germ lipase, both of which are inhibited by specific  $-\text{SH}$  reagents. The former enzyme was inhibited by *p*-chloromercuribenzoic acid to the same extent, regardless of the substrate used in the activity determination, as expected. However, when the lipase was incubated with *p*-chloromercuribenzoic acid for 20 minutes and subsequently tested on a series of 11 substrates of widely varied structure, the inhibition varied from 10 to 85 per cent, apparently depending upon the molecular size of the substrate. The variation was systematic and was correlated with the length of the alcohol or fatty acid and with the number of esterified hydroxyls. Arsenicals and oxidizing agents gave similar results. This observation is interpreted to mean that an enzyme may be inhibited by reagents selectively reacting with a protein group, this group itself not being directly involved in activity. This might occur by altering the special configuration of the protein around the "active center."

Colorimetric method for determination of phenol oxidase and peroxidase in plant tissues. FREDERICK G. SMITH (by invitation), WILLARD B. ROBINSON (by invitation), and ELMER STOTZ, N. Y. State Agric. Expt. Sta., Cornell Univ., Geneva, N. Y. A new colorimetric method for phenol oxidase (and peroxidase) has been developed of comparable accuracy to the manometric and chronometric methods of Nelson, Dawson, and coworkers but of greater simplicity and sensitivity. Reduced Na 2,6-dichlorobenzeneonemido 3'-chlorophenol is oxidized by phenol oxidase through the mediation of catechol, and directly by peroxidase and  $\text{H}_2\text{O}_2$ . The rate is determined photometrically by direct galvanometer deflections.

during a 15 to 45 sec interval after the reaction starts. With suitable concentrations of enzyme, leuco-dye, and catechol or  $H_2O_2$  the rates are linear for at least 60 sec with preparations from several plant tissues and are proportional to enzyme concentration over a ten-fold range. The substituted indophenol dye adopted was best of a number tested with respect to sensitivity and linearity of rates with phenol oxidase, and was roughly 300 and 90 times as sensitive as leuco-malachite green and pyrogallol, respectively, with peroxidase.

Phenol oxidase was usually prepared by thorough homogenization in the presence of ascorbic acid to stabilize the enzyme and precipitation by 80% acetone at  $-20^\circ C$  to remove excess ascorbic acid and other reducing materials. With some tissues, and especially for peroxidase, a simpler technic was possible.

The method is suitable not only for rapid, routine enzyme assay on a macro or micro scale but also on an ultra-micro level. With Lowry and Bessey's adaptation of the Beckman spectrophotometer, an amount of enzyme oxidizing 0.0002  $\mu M$  dye per min (equiv to about 0.002  $cm$   $O_2$  per min) can be determined.

**Vitamin A serum levels in Mongolism following vitamin A ingestion in oily and aqueous media.** ALBERT E. SOBEL, SIDNEY P. GOTTFRIED (by invitation) and BENJAMIN KRAMER. *Pediatric Research Lab and Dept of Biochemistry, The Jewish Hospital of Brooklyn, N. Y.* In children with Mongolism impaired intestinal absorption exists as indicated by low vitamin A absorption curves after feeding Oleum Percomorphum. These are even lower than those observed in our children with the Coeliac Syndrome.

**Vifort**, which is an aqueous dispersion of vitamin A (containing the vitamin B complex and vitamins C and D), an elevation of vitamin A in the blood serum was obtained. Upon administering an aqueous dispersion of Vitamin A similar to Vifort but containing no other vitamins a still greater rise was obtained.

Thus it appears that in Mongolism there is an impaired intestinal absorption of vitamin A in oil, which may be remedied (just as in children with the Coeliac Syndrome) when vitamin A is given in an aqueous dispersion.

**Response of the Heidenhain pouch to repeated application of eugenol.** HERBERT A. SOBER (by invitation), B. P. SONNENBLICK (by invitation) and FRANKLIN HOLLANDER. *Gastroenterology Research Lab, The Mount Sinai Hospital, New York City.* A homogenized 5 per cent eugenol-water suspension was introduced into a dog's Heidenhain pouch for 15 minutes. Following its removal, 4 successive 30-minute specimens of mucus secretion were collected. This cycle of

stimulation and collection was repeated, usually 6-7 times. The entire series was designated a "fatigue" experiment. Similar "follow-up" experiments, of shorter duration, were performed after 36 hours and 3-5 months. All specimens were examined for volume, pH, opacity, viscosity, color, blood content, specific gravity, per cent solids, and various cellular components. Five dogs have so far been used.

The results indicate that striking changes occurred during the initial 3 or 4 cycles. At first the mucosa secreted the usual opaque, jelly-like, whitish mucus. Thereafter there appears to be a decrease in mucus output, and dilution with a clear free-flowing sero-sanguinous material. At the end of the fatigue experiment, the specimens consisted essentially of bloody inflammatory exudate. In the follow-up experiments, inflammatory exudate was obtained sooner than in the fatigue experiment. This indicates that the protective barrier of the gastric mucosa had been impaired by repeated stimulation, and even after 3-5 months had not completely returned to its original state. Further evidence in support of the conclusions, based on cytological characteristics of the specimens, will be presented by Sonnenblick et al at this meeting. The implications of these findings for experimental gastric carcinogenesis will be discussed. [This investigation was conducted with the aid of a grant from the National Cancer Inst.]

**Free amino acids in cerebrospinal fluid.** J. D. SOLOMON (by invitation), S. W. HIER (by invitation), and OLAF BERGEIM. *Dept of Biological Chemistry, Univ of Illinois College of Medicine, Chicago, Illinois.* The microbiological determination of free amino acids in cerebrospinal fluid involves certain difficulties due to the low amino acid content and the presence of substances inhibiting the growth of the microorganisms employed. These difficulties were overcome by heat treatment and concentration of specimens. Specimens of spinal fluid were obtained from patients undergoing encephalography at the Illinois Neuropsychiatric Institute. The following amino acids were determined: arginine, histidine, isoleucine, leucine, phenylalanine, threonine, tyrosine, lysine and valine. Most of these amino acids, while present in spinal fluid in much lower concentration than in plasma or sweat, follow somewhat the same pattern. As in the case of sweat, arginine was somewhat exceptional. [Supported by grants from the Univ of Illinois Graduate School and The Nutrition Foundation, Inc.]

**Influence of repeated eugenol stimulation on the gastric mucosa as studied in mucus smears.** B. P. SONNENBLICK (by invitation), HERBERT A. SOBER (by invitation) and FRANKLIN HOLLANDER. *Gastroenterology Research Lab, The Mount Sinai*

*Hospital, New York City* Repeated stimulation of the gastric mucosa of Heidenhain pouches with 5 per cent eugenol suspension has been performed on 5 dogs. Similar but shorter "follow up" studies were done 36 hours and several months after these initial "fatigue" experiments. Sixty successive specimens of mucus secretion were collected during the experiments on any one animal. Smears were prepared from each specimen and stained with toluidine blue. For further experimental procedures and physiological characteristics see abstract by Sober et al.

Study of the preparations yields the following observations and conclusions: (1) Only columnar epithelial cells are observed in the earliest samples; thereafter, the amount of these drops with repeated stimulation. This drop parallels a diminution in mucin-like substances. (2) Metachromatically stained mucous neck chief cells make their first appearance later than columnar cells, as do leucocytes. (3) Parietal cells, in smaller quantity than others, are observed in most samples. At stages where other cell types are undergoing cytolysis, these are well preserved. (4) Blood, usually hemolyzed and staining greenish, increases with repeated irritation. (5) By the end of the fatigue experiment, the specimens contain few or no columnar and neck chief cells, and little or no mucin-like substances. Instead, they consist predominantly of inflammatory exudate with blood, fibrin, and leucocytes. (6) The follow up experiments indicate that the mucosa does not completely recover to its original untreated state after 3-5 months. These observations and conclusions are supported by those of Sober et al. Histological studies on dogs and rodents are now in progress. [This investigation was conducted with the aid of a grant from the National Cancer Inst.]

The effect of oxythiamine and some oxythiamine derivatives on mice. MORRIS SODAK (by invitation) and LEOPOLD R. CLAREDO. *Dept of Biochemistry, Fordham Univ., New York City*. Oxychlorothiamine hydrochloride (Buchman and Williams, *J. Am. Chem. Soc.*, 57: 1571 (1935)) and oxybromothiamine hydrobromide (from oxythiamine by treatment with 48 per cent hydrobromic acid at 150°C) were prepared with a view to elucidating the mechanism of the antagonistic action of oxythiamine hydrochloride (*J. Am. Chem. Soc.* 66: 1988 (1944)).

Mice were fed a synthetic thiamine deficient diet throughout. The supplements mentioned below were given daily by injection. Mice weighing 9 to 13 grams were depleted of thiamine stores and then maintained on one microgram of thiamine for one to two weeks. All mice continued to receive the thiamine supplement and in addition were given one of the following: 25, 50, or 90 micrograms of oxythiamine, 100 micrograms of oxychlorothia-

mine, or 130 micrograms of oxybromothiamine. Controls were maintained on thiamine alone. Growth inhibition was immediately manifest in almost every animal receiving oxythiamine. A hunched back, severe loss of appetite and weight, and eventual death resulted after varying lengths of time. The thiamine controls, as well as the mice on the thiamine plus oxychlorothiamine (12 mice) or oxybromothiamine (4 mice) continued to gain weight and maintained their appetite.

The results indicate that a free hydroxyl group on the side chain of the thiazole moiety of oxythiamine is necessary for the manifestation of an antagonistic action.

It is interesting to note that whereas oxythiamine produces as much color with the Prebluda-McCollum diazotized p-aminacetophenone reagent as does thiamine, neither oxychlorothiamine nor oxybromothiamine react with the reagent. [Aided by a grant from the John and Mary R. Markle Foundation.]

The enzyme synthesis of glutamine. JOHN J. SPECK (introduced by E. A. Evans, Jr.) *Dept of Biochemistry, Univ. of Chicago, Chicago*. An investigation of the enzymic synthesis of glutamine has been undertaken as an approach to the study of peptide bond synthesis. Dispersions of fresh pigeon liver and extracts of pigeon liver acetone powder have been used as sources of the enzyme system.

In fresh pigeon liver dispersions under aerobic conditions, glutamine is synthesized when glutamate and ammonia are added, but inorganic phosphate, magnesium and potassium ions, cytochrome, diphosphopyridine nucleotide, and an oxidizable substrate such as citrate or oxalacetate must also be added to achieve maximum rates in diluted dispersions. Adenosine triphosphate is inhibitory. In these preparations the synthesis is closely linked with oxidative reactions; the reaction proceeds more readily in oxygen than in air and does not occur at all anaerobically. Under the most favorable conditions thus far studied, the synthesis occurs at a rate of about 25 micromoles per 100 mg. fresh liver per hour, corresponding to a  $Q_{\text{glutamine}}$  of about 28. The fresh liver dispersions hydrolyze adenosine triphosphate very rapidly, glutamine is hydrolyzed more slowly.

Glutamine is synthesized in extracts of pigeon liver acetone powders when glutamate, ammonia, adenosine triphosphate, and magnesium ions are added. The reaction occurs more rapidly anaerobically than aerobically and is accelerated by cysteine. The extracts do not hydrolyze glutamine but hydrolyze adenosine triphosphate slowly.

It seems probable that the coupling of glutamine synthesis with oxidative processes in fresh liver dispersions involves the intermediate formation of high energy bonds in adenosine triphos-

phate and that the negative effects obtained with added adenosine triphosphate in these preparations is due to the extraneous enzymic reactions which do not occur in acetone powder extracts. The enzyme system involved in glutamine synthesis is similar to those involved in acetylation of choline and sulfanilamide. In all three cases adenosine triphosphate participates in the linking of a carboxyl and an amino group to form an amide, magnesium ions and cysteine accelerate the reaction, and the enzymes are present in extracts of acetone powders.

**In vitro methemoglobin reduction in intact erythrocytes** S S SPICER, C H HANNA, and ARIEL M CLARK (introduced by H D Baernstein) *National Inst of Health, Bethesda, Maryland*. Factors affecting the rate of methemoglobin (MHb) reduction have been studied in dog erythrocytes treated with  $\text{NaNO}_2$  and incubated at  $38^\circ\text{C}$ . The reduction rates thus obtained are expressed as the first order velocity constants  $\frac{\Delta \log [\text{MHb}]}{\Delta \text{time}}$ .

After washing the cells two times for 30 minutes in 10 volumes of normal saline there is no MHb reduction. Seven washings almost completely deplete the erythrocyte glucose and lactic acid and reduce the glutathione to one-third. Restoring the glucose level of washed erythrocytes to 100 mg per cent gives a rate about half that of whole blood. Further increases in glucose do not affect the rate. The rate with fructose is about half that with glucose and with galactose about half that with fructose. A rate slightly greater than that of whole blood can be obtained in washed cells with sodium lactate at a level of 1100 mg per cent. The rate of MHb reduction with a lactate concentration of 150 mg per cent is one-fourth that of normal. Malic and fumaric acids are as effective as lactic acid. Substrates which fail to bring about the reduction of MHb in washed erythrocytes include pyruvate, succinate, acetate, malonate, glutamate, and citrate. Large amounts of lactate, malate and fumarate added to whole blood do not appreciably increase the MHb reduction rate. Oxalate and citrate inhibit MHb reduction. Lactate overcomes the inhibition by oxalate.

**Physicochemical studies on water soluble chlorophyll derivatives** MONA SPIEGEL-ADOLF, *Dept of Colloid Chemistry, Temple Univ School of Medicine, Philadelphia, Pa*. With the help of a DU Beckman photoelectric quartz spectrophotometer the optical absorption power of a commercial chlorophyll preparation (chloresium) was studied before and after purification, at various concentrations within a range of 4200–2200 Å. An absorption peak lies between 4100–4000 Å corresponding to  $E = 1.17 \times 25$ . Two more peaks at lower wave lengths were observed in the unpurified sample only. Upon intensive irradiation with a

Hanovia mercury quartz lamp (8 hours at 40 cm distance) practically no changes were observed when the sample was kept in pyrex glass and therefore exposed to the visible part of the radiation only. On the other hand in a sample of 0.004% purified chloresium irradiated in quartz, a marked decrease of the above mentioned absorption peak was noticeable as well as higher light transparency in the lower wave lengths range. Increase in UV irradiation intensifies this phenomenon. In chloresium solutions of higher concentrations (0.02%) practically no changes became manifest upon irradiation with short-wave light.

Electrophoresis experiments using a Landsteiner-Pauli apparatus and photoelectric colorimeter show migration of the colored material to the positive pole without appreciable signs of fractionation. The influence upon metabolic processes of the water soluble chlorophyll derivatives was tested with the Warburg apparatus. The oxygen uptake neither of brain, liver, muscle of rat, nor that of suspensions of yeast cells was influenced by the presence of various concentrations of water soluble chlorophyll derivatives, even when the time of observation was extended up to five hours. [Aided by a grant from the Ryslan Corp.]

**Enzymatic action of the cerebrospinal fluid following electrically induced convulsions** M SPIEGEL-ADOLF, P H WILCOX (by invitation) and E SPIEGEL (by invitation) *State Hospital, Traverse City, Mich, and Depts of Colloid Chemistry and Exp Neurology, Temple Univ School of Medicine, Philadelphia, Pa*. In a preceding abstract changes of the extinction coefficient ( $E_{4150}$ ) in the cerebrospinal fluid (CSF) of schizophrenics following various types of electroshock treatment were reported. These changes were interpreted as indicating the presence of nucleic acids and related substances in the CSF. In order to elucidate the mechanism of these changes, the enzymatic power of the same CSFs upon samples of nucleic acids of animal origin was tested. The diminution in the optical absorption power of the latter (D) was measured with a Beckman photoelectric quartz spectrophotometer similarly as in our previous studies of cerebral concussion (Fed Proc 5 156, 1946). A comparison with the E measurements gave the following results. In nearly all untreated patients the D values were low irrespective of the original E values. Intensive electroshock treatment increased these values markedly. In some cases the increase of D preceded the one of E. Mild electroshock treatment produced in the majority of cases an initial rise, upon further treatment D usually again approached the initial value. Analogous studies with nucleic acids of plant origin gave in the majority of the cases similar results. Estimation of the lipase activity by a modification of Cherry and Crandall's method

showed only occasionally a slight rise. These experiments seem to indicate that enzymatic processes play a part in the genesis of the changes of nucleic acid metabolism of the brain which follow electroshock.

**Spectrophotometry of the cerebrospinal fluid before and after electrically induced convulsions.** M SPIEGEL-ADOLF, P H WILCOX (by invitation) and E A SPIEGEL (by invitation) *Traverse City State Hospital, Traverse City, Mich and Depts of Colloid Chemistry and Exp Neurology, Temple Univ Medical School, Phila, Pa.* Continuing studies of the effect of electroshock upon the cerebrospinal fluid (CSF) of dogs (Spiegel Adolf, Spiegel, Ashkenaz, Lee), CSFs of schizophrenics were analyzed by means of a Beckman photoelectric quartz spectrophotometer before and at various intervals after convulsions had been induced by electric currents. Selective absorption with a peak at  $2650 \text{ \AA}$  was found in the CSF of untreated schizophrenics. In 18 patients the mean extinction coefficient ( $E$ ) at  $2650 \text{ \AA}$  was  $2.0 \pm 0.5$ . Control studies on the CSF of patients without nervous and mental disorders and receiving no barbiturates gave in 28 cases an s shaped absorption graph with  $E(2650) = 1.24 \pm 0.59$ . The selective absorption is interpreted as indicating the presence of nucleic acids or their derivatives in the CSF. Following 3-10 convulsions induced by a low intensity current (modified half wave rectified 60 cycle current for 0.8-1.2 seconds), there was usually a slight decrease or no change of the  $E$  value and only occasionally a slight increase of the selective absorption. After application of a relatively high 60 cycle A C current for 0.3-0.5 seconds, there was in the beginning of the series (after 6 convulsions) a depression of the  $E$  values and only occasionally a rise or no change, at the end of the series (after 10 convulsions) an increase of the  $E$  value developed. This increase was also pronounced in CSFs tapped several days or weeks after the last convulsion. These observations are taken to mean changes in nucleic acid metabolism related to the electroshock convulsions.

**On the quantitative relationship between the concentration of calcium and the coagulation of the blood.** MARIO STEFANINI (by invitation), MARCEL C BLANCHARD (by invitation) and ARMAND J QUICK *Dept of Biochemistry, Marquette Univ School of Medicine, Milwaukee, Wisc.* By means of the resin, amberlite, the calcium of the blood can be removed, and by re adding known quantities of calcium chloride, the amount optimum for coagulation can be determined directly. Experimentally 4 parts of blood treated with amberlite were mixed with 1 part of an isotonic mixture of calcium chloride and sodium chloride. For human blood a concentration of 0.0012 to 0.005 M Ca appears optimum. Below 0.0006 M the

clotting time is markedly increased and at a concentration of 0.0003 M the blood often fails to clot. When the calcium concentration is increased above 0.005 M the clotting time is progressively delayed.

The minimum calcium concentration for optimum coagulation of dog and rabbit blood is somewhat higher than for human blood, namely 0.0018 M. Above 0.005 to 0.007 M Ca, inhibition appears. The coagulation time of recalcified whole blood is usually twice or three times as rapid as when determined by the Lee White method (due most likely to the release of a little thromboplastin in the manipulation).

When dogs are given sufficient dicumarol to elevate the prothrombin time from a normal of 6 seconds to 28-52 seconds, the minimum optimum or critical concentration of calcium was raised to 0.005 M, a concentration which is distinctly higher than the normal blood calcium level which is approximately 0.0015 M. This suggests that the prolonged clotting time in dicumarol poisoning is due not only to hypoprothrombinemia but also in part to an inadequacy of calcium. [This work was supported by a grant from the U S Public Health Service.]

**The excretion of porphyrin by pernicious anemia patients treated with pteroylglutamic acid.** RUTH C STEINKAMP (by invitation), CARROLL F SHUKERS (by invitation), JOHN R TOTTER, and PAUL L DAY *Dept of Biochemistry, School of Medicine, Univ of Arkansas, Little Rock.* Urine was collected from several patients with pernicious anemia and anemia accompanying leukemia, at two hour intervals after treatment with pteroylglutamic acid or injectable liver extract. In most cases the urine obtained during the second two-hour period after the initial treatment contained a considerable quantity of a red pigment which remained on the filter. In such cases the urinary output of pteroylglutamic acid during the first 24 hours was only 2 to 11% of the test dose. In contrast, no such pigment has been obtained from 12 normal individuals to whom the vitamin was administered, in these cases the urinary return of PGA was 24 to 38% of the dose.

The red pigment was purified by extraction with dilute ammonia, adsorption on  $\text{Ca}_3(\text{PO}_4)_2$  gel at slightly acid pH, and elution with dilute ammonia. After extraction of the acidified eluate with ether and reextraction into dilute HCl it gave a pronounced red fluorescence in ultraviolet light. The HCl solution showed marked absorption at  $403 \text{ m}\mu$ , indicating the porphyrin nature of the pigment. [Aided by grants from the Nutrition Foundation, Inc, and the Williams-Waterman fund of the Research Corporation. Lederle Laboratories, Inc supplied the pteroylglutamic acid.]

**A study on the availability of beta-methoprop-  
anol for growth purposes in the rat.** JAKOB A

STEKOL *Amino Products Research Division, Rossford, Ohio* The possibility that beta-methiopropanol might be available for growth purposes *in lieu* of either cystine or methionine was indicated by the fact that this substance was shown to be a decomposition product of methionine under the action of certain bacteria

We synthesized beta-methiopropanol from methyl mercaptan and trimethylenechlorohydrin and fed it to albino rats which were maintained on either low casein diets or diets in which the sole source of organic nitrogen was a mixture of amino acids and crystalline vitamins

The data obtained indicated that beta-methiopropanol failed to stimulate the growth of rats under the conditions under which either *L*-cystine or *DL*-methionine was effective

Studies on desoxyribonucleoproteins isolation and properties of genoprotein T KURT G STERN, G GOLDSTEIN (by invitation), J WAGMAN (by invitation), and J SCHRIYER (by invitation) *Dept of Chemistry, Polytechnic Inst, Brooklyn, N Y* Chromosin, as prepared from calf thymus by extraction with 1 M NaCl solution according to Mirsky and Pollister, has been shown (Fed Proc 5 156, 1946) to represent essentially a mixture of free sodium thymonucleate and histone chloride

The desoxyribonucleoprotein of thymus tissue has now been obtained in what appears to be the *native* state The method of isolation utilizes the inhibition, by sodium arsenate, of nucleodepolymerase activity (F G Fischer, I Boettger, and H Lehmann *Lehmann Z physiol Chem* 271 246 (1941)) as well as the solubility of the nucleoprotein in water and its insolubility in 0.14 M NaCl solution After removal of aggregated material by high speed centrifugation a highly purified preparation is obtained which behaves as a homogeneous substance in the analytical ultracentrifuge and in the electrophoresis apparatus The fairly compact particles possess a molecular weight of the order of a million The solutions of the nucleoprotein in water or neutral phosphate buffer of low ionic strength exhibit a low viscosity and no appreciable flow birefringence Thixotropic non birefringent gels may be obtained directly from thymus tissue by water extraction and from purified solutions of the nucleoprotein by precipitation with 0.14 M NaCl It is probable that the material exists in the chromosomes in the gel state

In order to distinguish this native nucleoprotein from artifacts such as chromosin and in view of its presumed relationship to the genes, the name *Genoprotein T* (for thymus) is proposed for it

The origin of certain fetal metabolites DEWITT STETTIN, JR., and WILLIAM H GOLDWATER (by invitation) *Dept of Biochemistry College of Physicians and Surgeons, Columbia Univ* The addition of isotopically labeled fatty acids or

cholesterol to the diets of pregnant rats resulted in the appearance of isotope, in significant concentrations, in the corresponding products isolated from the fetuses, indicating transplacental migration of these materials The rate of incorporation of deuterium into fetal glycogen, fatty acids, and cholesterol has also been determined after enrichment of the body fluids with deuterium oxide Comparison of the values obtained with analogous values secured from products isolated from the maternal livers indicated that all three of these substances were rapidly being synthesized in the fetuses Analysis of the data further revealed that in the 19-day rat fetus the quantity of glycogen synthesized and deposited per day was approximately equal to the total quantity contained in the fetus This is in contrast to the situation in the adult rat where it was shown that in the liver, about 70%, in the carcass, only 20% of the glycogen was replaced by newly synthesized glycogen each day [Aided by grants from the Josiah Macy, Jr, Foundation and the Nutrition Foundation, Inc]

Phosphorylated carbohydrate compounds in developing chick embryo P K STUMPF (introduced by H B Lewis) *Virus Lab, Dept of Epidemiology, School of Public Health, Univ of Michigan, Ann Arbor, Mich* The results of an analysis of the whole chick embryo for the presence of six phosphorylated intermediates formed in the breakdown of glucose would appear to support the contention of Meyerhof that even the developing chick embryo in its 6-8-10 day stages of growth has phosphorylation mechanisms similar to if not identical with those found in bacteria and in plant and animal tissues These results would thus contradict the findings of Needham who contends that glucose is broken down by a nonphosphorylating mechanism in the early growth stages of the chick embryo

Trichloroacetic acid extracts of whole six, eight, and ten day chick embryos were fractionated to yield a barium insoluble fraction and a barium soluble alcohol insoluble fraction, employing the procedure developed by Umbreit and his group In the first fraction were found fructose-1,6 diphosphate, phosphoglyceric acid, and adenosine diphosphate, and in the second fraction glucose-1-phosphate, glucose 6-phosphate, fructose 6-phosphate Since these esters were found in approximately the same concentrations in the three different age groups of chick embryos, it was concluded that the phosphorylation mechanisms were already well established by the sixth day of development, and that because of the presence of these compounds, glucose or glycogen was being metabolized probably by the usual phosphorylative pathways

The effect of viral infection on these phosphorylation patterns was also studied The phosphorylation pattern which consisted of the six phosphorylated

compounds was not significantly altered after the chick embryo had been infected for 48 hours either with PR8 strain of influenza virus Type A or with swine influenza virus [ aided by National Foundation for Infantile Paralysis ]

Influence of insulin on glycogen synthesis and breakdown in liver slices EARL W SUTHERLAND (by invitation) and CARL F CORI Dept of Biochemistry, Washington Univ School of Med, St Louis When thin slices of rabbit or rat liver are incubated in two per cent glucose-1 phosphate and 0.05 M NaF, a rapid synthesis of glycogen can be demonstrated in the slices themselves, amounting to one per cent per hour or more Addition of insulin accelerates the glycogen synthesis The inorganic phosphate which appears in the medium parallels the formation of glycogen and is increased by the addition of insulin When liver slices of fed animals are incubated in phosphate buffer instead of glucose-1-phosphate, the phosphorylase activity is in the direction of glycogenolysis Under these conditions insulin, confirming Shipley and Humel,<sup>1</sup> increases the glucose output of liver slices and causes a more rapid disappearance of glycogen The acceleration of glycogenolysis is more marked in rabbit than in rat liver slices Disruption of cell structure by freezing or grinding results in disappearance of the insulin effect Nearly maximal effect on glycogenolysis is given by 0.005 to 0.01 mg of native insulin per cc and by 0.015 to 0.03 mg of certain cleavage products obtained by mild treatment of insulin with alkali Such products could not be obtained from other proteins

These observations suggest that insulin has an accelerating effect on the phosphorylase activity in the liver and that its effect on the glycogen level will depend on whether phosphorylase activity proceeds in the direction of synthesis or breakdown of glycogen

The excretion of sulfanilamide derivatives after oral administration to white rats ELIZABETH TAYLOR (by invitation), FRED H SNYDER (by invitation), and FRED W OBERST Dept of Biochemistry, Research Lab, The Wm S Merrell Co, Cincinnati Studies have been carried out on the route of excretion of twelve derivatives of sulfanilamide following oral administration to white rats Analyses were made on urine and on fecal extracts by the colorimetric method of Bratton and Marshall Extracts of feces were prepared by Soxhlet extraction with acetone or, in the case of compounds having carboxylic or sulfonic acid groups, by extraction with 2 per cent sodium hydroxide Since most of the compounds studied were substituted in the N-4 position, a preliminary

acid hydrolysis procedure was used routinely before colorimetric estimation

Ten of the compounds studied (N-(4-aminobenzenesulfonyl) 2-phenylpropylamine, N-(4-aminobenzenesulfonyl) N-methyl 2-phenylpropylamine, N-(4-aminobenzenesulfonyl) ephedrine, 4-sulfonamidodiphenylthiourea, tartarylsulfanilamide, diacetyltartarylsulfadiazine, diacetyltartarylsulfathiazole, sodium propionylsulfanilamide- $\beta$  sulfonate, sodium propionylsulfathiazole  $\beta$  sulfonate, sodium sulfobenzoylsulfathiazole) were found to be excreted largely in the feces, one (2-(4-aminobenzenesulfonyl)acetamide) appeared primarily in the urine, and one (N-(4-acetylamino-benzenesulfonyl)-N-methyl-2-phenylpropylamine) was rather equally divided between the two

Two compounds, 4-isothiocyanobenzenesulfonylguanidine and 2-(4-isothiocyanobenzenesulfonylamido)pyrimidine, gave theoretical results when hydrolyzed in pure solution and determined by the colorimetric method They could not, however, be recovered quantitatively after addition to normal rat feces or to acetone extracts of feces

The purification of phosphofructokinase from rabbit muscle JOHN FULLER TAYLOR Dept of Biological Chemistry, Washington Univ School of Medicine, St Louis Aqueous extracts of minced rabbit muscle contain the enzyme, phosphofructokinase, which catalyzes the reaction  
Adenosinetriphosphate + fructose 6 phosphate  $\rightarrow$  adenosinediphosphate + fructose 1,6-phosphate  
The reaction can be followed manometrically by the liberation of CO<sub>2</sub> from bicarbonate buffer Mg<sup>++</sup> is required

The protein fraction precipitated between 0.4 and 0.5 saturation with ammonium sulfate at pH 7.5 contains a considerable part of the enzymatic activity and shows a specific activity that may be as high as ten times that of the original extract As much as threefold further purification has been achieved by refractionation with ammonium sulfate Fractionation with acetone has not been successful because extensive destruction easily occurs The use of aluminum hydroxide is of some value in removing material that interferes with the test used without adsorbing much of the enzyme

Enzyme preparations lose activity slowly at pH 7.5 but are rapidly inactivated at pH 6 Dialysis can be carried out against water or dilute salt solutions if the pH of the enzyme solution remains about 7.5 Extraction of the minced muscle with weak alkali (0.03 N NaOH) increases the yield of phosphofructokinase, probably because the pH of the extract is higher

The enzyme appears to be considerably less than 1 per cent of the extractable protein Total enzymatic activity is not recovered in the ammonium

<sup>1</sup>Shipley R A and Humel E J, Am J Physiol 144 51 (1945)



sulfate fractions, conditions that affect the stability and activity are being investigated

**Estimation of parathyroid hormone activity by its effect on serum inorganic phosphorus in the rat** HELEN M. TEPPERMAN (by invitation), MAURICE V. L'HEUREUX (by invitation), and ALFRED E. WILHELM *Dept of Physiological Chemistry, Yale Univ, New Haven, Conn* Evidence is presented to show that the subcutaneous injection of parathyroid hormone into male albino rats (weight range 150-250 grams) in the post-absorptive state brings about in 3 hours a fall in serum inorganic phosphorus which is directly proportional to the logarithm of the dose of hormone administered (in U S P units) In setting up a dose-response curve based on this relation it is observed that there is an effect of initial level of serum inorganic phosphorus on fall in serum inorganic phosphorus at each dose level of hormone used It is shown that this effect is consistent and may be adjusted for It is therefore possible to establish a standard dose-response curve which may be used to carry out simple and rapid estimations of parathyroid hormone activity in unknown preparations An example is also given of an assay employing 12 rats in a more rigorous design—the "symmetrical pairs" design of Yates—which demonstrates that the rat serum inorganic phosphorus method is comparable in reliability and accuracy to the dog serum calcium method, employed in the same design, for the estimation of parathyroid hormone

**Rearrangement of steroid ring C ketols in alkali** CHARLES TESAR (by invitation), EVELYN BORGSTROM (by invitation), J. R. XENOS (by invitation) and T. F. GALLAGHER *Dept of Biochemistry, Univ of Chicago, Chicago, Illinois* Because of their importance in the partial synthesis of adrenal cortical steroids, a detailed investigation of the reactions of the ring C ketols derived from both cholic and desoxycholic acids has been made The ring C ketols of the cholic acid series were obtained by low temperature hydrolysis of the 11( $\alpha$ ) bromo 12 keto derivative followed by isomerization with boiling alkali The reaction yielded two principal products which have been identified as 3( $\alpha$ ),7( $\alpha$ ),11( $\alpha$ ) trihydroxy-12-ketocholanic acid and 3( $\alpha$ ),7( $\alpha$ ),12( $\beta$ ) trihydroxy-11-ketocholanic acid This rearrangement is similar to that which occurs when 3( $\alpha$ ),12( $\beta$ ) dihydroxy-11-ketocholanic acid is heated in alkali All four possible isomeric ketols are obtained but the 11( $\alpha$ ) hydroxy 12-keto and the 11 keto 12( $\beta$ )-hydroxy derivatives constitute at least 90 per cent of the reaction product The rates of saponification of the acetoxy methyl esters and the behavior of the isomers and their derivatives toward ketonic reagents have been studied These reactions provide a basis for the structure of the products

obtained in the cholic acid series, the structure of the ketols of the desoxycholic acid series has been proven by independent methods

**A study of experimental variables in the bacteriological determination of amino acids (microbiological assay)** GERRIT TOENNIES and DOROTHY LEAF GALLANT (by invitation) *Lankenau Hospital Research Inst and Inst for Cancer Research, Philadelphia 30, Pa* Difficulties encountered in the determination of amino acids with *S. faecalis* (Stokes, Gunness, Dwyer and Caswell, *J Biol Chem* 160 35 (1945)) on tissue protein preparations of high nucleic acid content induced the authors to investigate certain factors influencing bacterial growth, such as method of cleaning of assay tubes, length of sterilizing time, stability of vitamins, type of inoculum, concentration of glucose, kind and concentration of buffers, length of incubation period, and presence of nucleic acid hydrolysates, ammonia and other accessory nutrients Use of a heavily buffered medium (0.3 M phosphate of pH 6.5, and 2% glucose) in conjunction with photoelectric turbidity measurements (at a mean wave length of 700 millimicron where color effects are at a minimum) resulted in growth responses nearly linearly proportional to the concentration of the limiting amino acid, and concomitant substantial gains in analytical precision Other modifications found conducive to increased consistency and accuracy are treatment of assay tubes with hot chromic-sulfuric acid and subsequent repeated autoclavings in distilled water, sterilization for about 3 minutes (120°), inoculation with a culture which has been kept quiescent at low temperature for several days, and some modifications of the medium, including supplementation with ammonium ion and a hydrolysate of yeast nucleic acid and thymine Compared with the stability of biotin toward acid hydrolysis its dilute aqueous solutions appeared to be highly labile even at 2°

Experimental records demonstrating the role of the variables mentioned will be presented, together with results of the practical application of a modified method

**Studies on the function of pteroylglutamic acid in *Streptococcus faecalis*** JOHN R. TOTTER and EDITH S. SIMS (by invitation) *Dept of Biochemistry, School of Medicine, Univ of Arkansas, Little Rock* *Streptococcus faecalis* (American type culture collection No. 8043) was grown in the usual way but with KCN or H<sub>2</sub>O added aseptically after sterilization of the medium Growth was determined at various times by measuring turbidities

In a typical experiment it was found that 0.0125 N KCN reduced the 40 hour growth of the organism to one half maximum when 10  $\mu$ gm/ml of pteroylglutamic acid (PGA) was used as a stimulant Equally good growth resulted with 0.025 N

KCN when 10  $\mu$ gm/ml of thymine was used in place of PGA. Under similar conditions 0.13% H<sub>2</sub>O reduced the 40 hour growth to one half with PGA, while only 0.10% H<sub>2</sub>O was required with thymine. At levels of inhibitor above those stated the differences were more striking. The actual concentrations of inhibitor required to limit growth were somewhat variable but considerable alteration in the amount of thymine or PGA did not materially affect the results.

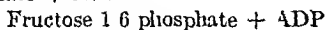
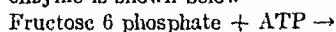
Subculture of the organism which grew in the KCN containing media frequently showed the presence of an unstable variant of *S. faecalis* which was capable of growing in the absence of PGA. This variant differed from the original organism in having lost its requirement for glutamic acid and PGA, in being resistant to KCN, and in being strongly resistant to sulfadiazine in the absence of added PGA or thymine. It was very susceptible to inhibition by H<sub>2</sub>O.

The data suggest that PGA is involved in the production of KCN sensitive enzymes, probably of the metallo-porphyrin group. [Aided by a grant from the Williams-Walterman fund of the Research Corporation.]

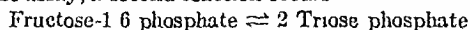
**Inactivation of phosphohexokinase in brain.** M. F. UTTER, Dept. of Biochemistry, Western Reserve Univ. In studies on mouse brain homogenates, it was noted that the ability of the preparations to form lactic acid from glucose was rapidly lost during the handling procedures involved in the ordinary Warburg techniques. The inactivation was greatly influenced by pH, increasing as the pH was lowered. More than 90 per cent of the glycolytic activity was lost in 10 minutes, if the brain homogenate was incubated at 38°C. at pH 6.4 or below.

Although glucose no longer served as a substrate for the inactivated preparation, hexosediphosphate was utilized, suggesting that the enzymes affected were concerned with the phosphorylation processes. Also, the addition of fructose 6-phosphate to the brain preparation prevented inactivation, lending further support to such a hypothesis.

Because of these observations, an assay was devised to permit measurement of the enzyme, phosphohexokinase. The reaction catalyzed by this enzyme is shown below:



In the brain homogenate under the conditions of the assay, a second reaction occurs:



By measuring the triose phosphate formed by brain homogenates from ATP and fructose 6-phosphate under specific conditions, it is therefore possible to determine the concentration of phosphohexokinase. By this assay it was shown that phosphohexokinase was almost completely inactivated in brain homogenates after incubation at

pH 6.4 or lower. Under certain conditions, the preparation can be reactivated by the addition of boiled brain homogenate, suggesting that at least part of the inactivation involves a heat stable factor.

**The influence of dietary protein upon the regeneration of liver protein in the rat.** HARRY M. VARS and FRASER N. GURD (by invitation), Harrison Dept. of Surgical Research, Schools of Medicine, Univ. of Pennsylvania, Philadelphia. The composition of the regenerating liver after partial hepatectomy has been studied in 250 grams male Wistar rats at 5 intervals after operation up to 14 days. Two series were studied: normal animals fed a diet containing 18% casein before and after operation, and protein starved animals fed a non-protein diet from 14 days before operation until sacrifice. The normal rats formed 0.37 gram of new liver protein per 100 grams of body weight in 14 days; the protein-starved formed 0.17 gram. The rate of liver protein production was most rapid in the first two post-operative days, and more rapid in the protein starved rats than in the casein-fed rats during this period.

The combination of pre-operative protein depletion plus 69.4% hepatectomy produced a net reduction of liver protein of 83%. Rats so prepared were used to study the effect of varied levels and types of dietary protein fed ad libitum for 14 days after operation.

The degree of regeneration of liver protein which occurred in the protein starved rats was greatly enhanced by postoperative protein feeding, in proportion to the level and biological value of the protein fed. Zein (10%) was no more effective than the non-protein diet. Fibrin (10%) was better than 10% wheat gluten. Casein at 5, 10, 18 and 27% levels gave increasing increments of new liver protein. The inclusion of methionine appeared to augment consistently the effect of casein alone.

**The amino acid composition of d-glyceraldehydephosphate dehydrogenase and aldolase from rabbit skeletal muscle.** SIDNEY F. VELICK and ETHEL RONZONI, Dept. of Biological Chemistry, Washington Univ. Medical School, St. Louis. Crystalline aldolase<sup>1</sup> and d-glyceraldehydephosphate dehydrogenase<sup>2</sup> may be obtained in good yield from rabbit skeletal muscle in essentially homogeneous form. These proteins have molecular weights of the same order of magnitude (sedimentation velocity and diffusion) and do not contain readily dissociable prosthetic groups. Samples of the enzymes, five times recrystallized and extensively dialyzed against distilled water, have been subjected to complete elementary and amino acid

<sup>1</sup> Taylor, John Fuller Green, Arda Alden and Cori Gerty T. Fed. Proc. 3, No. 1, March 1946.

<sup>2</sup> Cori Gerty T., Stein, Milton W. and Cori, Carl F. Jour. Biol. Chem. 159, 565 (1945).

analysis The minimum molecular weight of aldolase is 140500 and of d glyceraldehyde phosphate dehydrogenase 150000 calculated from amino acid analyses The chief differences between the two proteins are in the contents of glutamic and aspartic acids, leucine, valine, and phenylalanine In the case of the other amino acids minor differences occur Both proteins are relatively high in their content of basic and hydroxy amino acids The figures for aldolase approach the theoretical maximum based upon nitrogen content D-glyceraldehydephosphate dehydrogenase does not appear to be completely accounted for in terms of the known amino acids

Amino acid analyses on many independent enzyme preparations agreed within the limits of experimental error Microbiological methods were employed extensively and several amino acids were determined with two different organisms In addition chemical methods were employed where satisfactory micro procedures were available Control analyses of crystalline preparations of bovine serum albumin, insulin and  $\beta$  lactoglobulin agreed closely for the most part with the best published data

Further studies of the enzymes of normal and leucemic mouse liver homogenates CARL S VESTLING, RICHARD E MAXWELL (by invitation), JESSE N WILLIAMS, JR (by invitation), and HENRI QUASTLER (by invitation) *Division of Biochemistry, Noyes Lab of Chemistry, Univ of Illinois and the Dept of Radiology, Carle Hospital Clinic, Urbana* A preliminary report from this laboratory (J Biol Chem 165 385 (1946)) has indicated the failure of unwashed liver homogenates from leucemic mice (C-58 MacDowell strain) to oxidize octanoate in Lehninger-type systems (A L Lehninger, J Biol Chem 157 363 (1945)) Further work with washed homogenates in the presence of malonate has now yielded a similar result These experiments support the idea that the liver cells in an organ infiltrated by malignant leucocytes are enzymatically deficient However, an alternative explanation must be considered Since it has been shown that prolonged homogenization leads to failure to oxidize fatty acids, the possibility of increased cell fragility in leucemic livers must be tested A comparative study of "cytolysis quotients" (V R Potter, J Biol Chem 163 437 (1946)) in normal and leucemic liver homogenates is being carried out

Because of the involvement of cytochrome c in fatty acid oxidation by liver homogenates an investigation of the cytochrome oxidase activity of leucemic liver systems has been carried out It has been shown that there is no significant impairment of cytochrome oxidase activity in homogenates from C-58 leucemic mice

In certain of the experiments "cytolysis quo-

tients" and succinoxidase levels have been determined The results show a slightly higher succinoxidase activity in normal C-58 mice than in leucemic animals The studies reported are being extended so that further information concerning the enzymatic activity of infiltrated organs may be obtained

Investigations of the growth metabolism of normal and mutant imaginal discs of insects CLAUDE A VILLEE (introduced by A Baird Hastings) *Dept of Biological Chemistry, Harvard Medical School* The Cartesian diver ultramicrorespirometer provides a means of analyzing the metabolism of the particular group of cells in a larva (the imaginal disc) which will form a particular adult organ Previous work (Proc Nat Acad Sci 32 241, 1946) showed that normal wing discs have a  $QO_2$  of 20, "vestigial" wing discs a  $QO_2$  of 9 On the hypothesis that each gene regulates a particular biosynthesis, a search for the enzyme affected by the "vestigial" gene has been made by adding inhibitors or substrates to the buffer solution containing the disc in the diver Normal and "vestigial" disc respiration is inhibited by cyanide and azide and thus is mediated by an iron or copper porphyrin system, probably cytochrome-cytochrome oxidase Respiration is also inhibited by the hydroxynaphthoquinones SN-5949 and SN-5090, believed to inactivate some enzyme between cytochrome b and c Preliminary experiments show that pyruvate, but not succinate or lactate, increases "vestigial" disc respiration slightly The inhibition of normal and "vestigial" disc respiration by  $10^{-3}$  M iodoacetate is partially released by 0.2 M malate but not by 0.5 M succinate The respiration of "vestigial" discs is increased to that of normal discs by ascorbic acid and to a lesser extent by p-phenylenediamine and hydroquinone

These experiments indicate that the respiratory enzymes of the developing imaginal discs of insects are similar to those of a wide variety of cells from bacteria to mammals, that the cytochrome oxidase system of "vestigial" is normal, and that the "vestigial" gene affects some enzyme below cytochrome c in the respiratory chain

The synthesis and biological properties of some new thymine and uracil nucleosides DONALD VISSER, IRVING GOODMAN and KARL DITTMER (introduced by Robert C Lewis) *Univ of Colorado, Boulder* Since Loring and Pierce found that certain natural nucleosides were more effective than the corresponding free pyrimidines or purines for growth promotion of specific neurospora mutants (J Biol Chem 153 61-69, 1944, 160 409-15, 1945), it seemed desirable to synthesize a number of uracil and thymine nucleosides and to test them for possible growth promoting or growth inhibiting effects

1-D Ribosidouracil, 1-D arabinosidouracil, 1-D-galactosidouracil and 1-D glucosidouracil were prepared according to the original directions of Hilbert and Johnson (J Am Chem Soc 52 4489, 1930)

The 5 bromo- and 5 chloro derivatives of all four glycosidouracil compounds were prepared. The 1 glycosido 5 bromo uracils were prepared according to the method described by Hilbert and Johnson for the preparation of 5 bromo glucosidouracil. The 5 chloro glycosido uracils were synthesized by adding a slight excess of chlorine dissolved in carbontetrachloride to either the acetoglycosido-1-ethoxyuracils in carbontetrachloride or to the glycosidouracils dissolved in glacial acetic acid. Both procedures produced good yields of the chloro derivatives.

The Thymine glycosides were synthesized from the proper bromoacetate sugar and an excess of 2,4,-diethoxythymine with a few drops of pyridine added. Without isolating the intermediate, the free thymine glycosides were obtained by HCl hydrolysis of the aceto glycosido ethoxy thymine in methanol. By this method 1-D ribosidothymine, 1-D-arabinosidothymine, 1-D galactosidothymine, and 1-D glucosidothymine were prepared. The physical properties of these compounds will be discussed.

These compounds were tested on microorganisms for their growth promoting and growth inhibiting properties. For a uracil deficient mutant of *E coli*, the synthetic uracil and thymine nucleosides were neither growth promoting nor growth inhibiting. Results with other microorganisms will be presented.

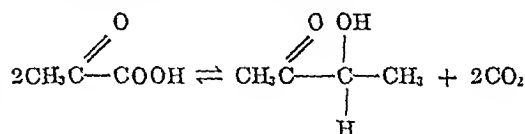
The antimetabolite effect of the optical isomers of the sulfoxide derived from methionine HEINRICH WÄLSCH and ERNEST BOREK (by invitation) Depts of Biochemistry, New York State Psychiatric Inst and Hospital and Columbia Univ, New York. The sulfoxide derived from d,l methionine is an effective antimetabolite against glutamic acid in the metabolism of *Lactobacillus arabinosus*. Since the compound contains two asymmetric atoms it exists as four stereoisomers. The antimetabolite activities of the diastereoisomers derived from l methionine (kindly supplied by Dr T F Lavine) differed by a factor of 2.5 which shows an enzymic sensitivity to the asymmetry of the sulfur atom. The mixture of diastereoisomers derived from l methionine is approximately seven times as active as that derived from d methionine. Therefore, it appears that the configuration of the carbon is of greater importance than that of the sulfur in determining the antimetabolite activity of the sulfoxide derived from methionine. The sum of antimetabolite activities of the component isomers is equal to that of the inactive material.

Stability of prothrombin ARNOLD G WARE (by

invitation), M MASON GUEST and WALTER H SEEGER, Dept of Physiology, Wayne Univ, Detroit, Mich. Ovalated bovine plasma retains 80 per cent of its prothrombin activity for 30 days at 5°C (2 stage assay). Ovalated plasma which has been dried from the frozen state, reconstituted, and neutralized with imidazole buffer exhibits similar stability characteristics. Prothrombin can be partially purified, as product type No 8 (Arch Biochem 6 85 (1945)), with the same percentage yield from either stored or fresh plasma. Such products are stable in saline solution for more than 24 hours at room temperature.

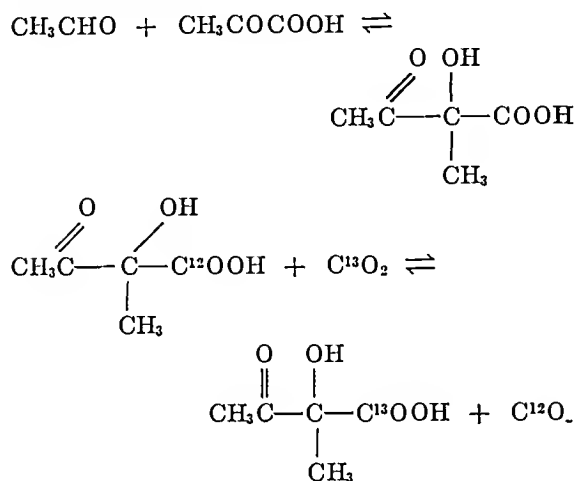
If prothrombin is purified so that it has a specific activity of 14,000 to 15,000 units per mg tyrosine, it possesses very poor stability characteristics in saline solutions. From 20 to 50 per cent of the activity is lost in 1 hour at 28°C. On longer standing significant amounts of thrombin appear, however, the thrombin formed amounts to less than 1 per cent of the original prothrombin activity. If such purified preparations are dissolved in ovalated plasma they are stable. The plasma stabilizing factors are removed late in the purification process. Crystalline bovine plasma albumin is not a stabilizing agent. (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> is a moderately effective stabilizer. [Aided by a grant from the National Institute of Health.]

α-Acetolactic acid, an intermediate in acetyl-methylcarbinol formation DEAN WATT (by invitation) and LESTER O KRAMFIZ, Dept of Biochemistry, Western Reserve Univ, Cleveland. C<sup>13</sup>O<sub>2</sub> is fixed in significant amounts in the carboxyl group of pyruvic acid during the conversion of the acid to acetyl-methylcarbinol (AMC) by cell suspensions of *Staphylococcus aureus*.



The presence of the isotope in the pyruvic acid indicates the reversibility of the reaction. Previous work has shown no direct evidence of the reversibility of α keto acid decarboxylation. Reversibility has only been demonstrated in β keto acids. The fixation of C<sup>13</sup>O in pyruvic acid by *Staphylococcus aureus* would appear to be an exception. The view that acetaldehyde is the sole precursor of AMC is not tenable with results obtained by several investigators who have shown that the rate of AMC formation is accelerated in the presence of both acetaldehyde and pyruvic acid. It is suggested that pyruvic acid and acetaldehyde condense as an intermediate in the reaction. The possibility that this intermediate is α acetolactic acid has been investigated. If this acid were the intermediate, fixation would occur as the conventional β-keto

acid fixation with subsequent splitting into pyruvic acid and acetaldehyde. The carboxyl group of pyruvic acid would contain heavy carbon under these conditions



The  $\alpha$  acetolactic acid was synthesized by oxidation of the labile hydrogen of methyl acetoacetic ester with subsequent hydrolysis

Investigations have shown that *Staphylococcus aureus* contains an enzyme which rapidly decarboxylates the acid into A M C and carbon dioxide. The enzyme is heat labile, five minutes at 100°C being sufficient to bring about its destruction. The decarboxylation is cocarboxylase independent and  $\text{Mn}^{++}$  dependent, as is the decarboxylation of other  $\beta$  keto acids such as oxalacetic and oxalosuccinic.

Attempts are being made to show the reversibility of the decarboxylation using  $\text{C}^{13}\text{O}_2$ .

Effect of cystine, lysine, and tryptophane on the growth of rats ingesting certain carcinogenic agents. JULIUS WHITE and FLORENCE R. WHITE, National Cancer Inst., National Inst of Health, United States Public Health Service, Bethesda, Maryland. Previous reports have indicated that the retardation of growth of young rats by the oral administration of certain carcinogenic agents could be overcome by incorporation of cystine or methionine in the diet still containing the carcinogen. The purpose of this study was to determine whether other essential amino acids would have the same effect as cystine or methionine. Three diets were prepared in which the cystine, lysine and tryptophane contents respectively were restricted to such an extent as to allow young rats to gain weight at a rate of about 1.5 gm per day. Weanling rats were placed on these diets and when they had reached a weight of 75-90 grams, 60 mg of ether, 1,2 benzantracene, 1,2,5,6 dibenzanthracene or *p* dimethylaminoazobenzene was added to each 100 grams of the respective diets. Animals on the cystine restricted diet showed marked retardation in growth although the food intake was equivalent to that ingested before the carcinogen

had been added. The addition of cystine to the diet still containing the carcinogen resulted in a prompt stimulation in growth. Rats ingesting the diets restricted in either lysine or tryptophane showed no retardation in growth when any of the carcinogenic agents studied were added. The significance of the specificity of cystine in stimulating growth of animals retarded by these carcinogenic agents will be discussed.

**Yeast metaphosphate.** J-M WIAIME (introduced by Carl F. Cori), Dept of Biochemistry, Washington Univ., School of Medicine, St. Louis. Metaphosphate accumulates in yeast under the condition previously described.<sup>1</sup> It can be determined quantitatively by extraction of the yeast with trichloroacetic acid, removal of the excess acid by extraction with ether and precipitation as the barium salt at pH 4.2 to 4.4. It can also be determined by extraction of the yeast with N sodium hydroxide, followed by depolymerization of the extracted ribonucleic acid with ribonuclease and precipitation with barium as described above. Good agreement was obtained between the two methods of extraction. The P content of the yeast metaphosphate was 19.6% as compared to a value of 19.8% for chemical hexametaphosphate, when isolated by the same method.  $\text{NaN}_3$  ( $2.5 \times 10^{-1}$  M) completely inhibited metaphosphate formation in yeast without affecting glucose fermentation.

The diffusion constant of the metaphosphate obtained by trichloroacetic acid extraction and alcohol precipitation was similar to that obtained for chemical hexametaphosphate. However, the barium salt, after conversion to sodium salt, gave a lower diffusion constant. Furthermore, when it was treated with toluidin blue and centrifuged, the supernatant fluid had a purplish (metachromatic) color, whereas when the same procedure was carried out with chemical hexametaphosphate or with metaphosphate prepared from yeast by alcohol precipitation, the supernatant fluid did not give a metachromatic color. These results suggest that the metaphosphate exists in the cell as a polymer of a hexametaphosphate unit.

**The metabolic fate of radioactive lactate in the phlorhizimized animal.** D. W. WILSON, ADELAIDE M. DELLUVA (by invitation) and SAMUEL GURIN, Dept of Physiological Chemistry, School of Medicine, Univ of Pennsylvania, Philadelphia. Sodium Lactate containing  $\text{C}^{14}$  in the  $\alpha$  and  $\beta$  positions was administered to a fasted phlorhizimized rat. 75 to 80 per cent of the lactate was apparently converted to urinary glucose and could be accounted for as "extra" sugar. Approximately 25 per cent of the administered radioactivity was recovered in the isolated urinary glucose.

The ketone bodies of the urine were fractionated

<sup>1</sup> J-M Wiame, Bull Soc Chim Biol 28:552 (1946)

by standard procedures. Carbon dioxide samples representing the carboxyl groups of acetoacetate and  $\beta$ -hydroxybutyrate were obtained. The acetone fractions were separately collected as the mercury complex. All of these fractions were radioactive and accounted for approximately 10 per cent of the administered radioactivity. The carboxyl carbons and the carbon of the acetone samples contained equal concentrations of  $C^{14}$ . It is apparent therefore that the lactate was converted to an appreciable extent to acetoacetate and  $\beta$ -hydroxybutyrate, and that all four carbon atoms were radioactive.

Approximately 20 per cent of the administered radioactivity was recovered in the respiratory  $CO_2$  collected during the first four hours of the experiment. An appreciable amount of radioactivity was likewise recovered in the liver and carcass fat as well as in the protein.

Since a significant portion of the lactate has been converted to ketone bodies, fat, protein and carbon dioxide, it is probable that the excretion of "extra" urinary glucose in almost quantitative amounts must be accounted for by a sparing action of the lactate upon some metabolite which would ordinarily be converted to ketone bodies and perhaps to fat in this type of experimental animal.

A mucolipoprotein in normal human plasma. RICHARD J. WINZLER, ARTHUR W. DEYOR (by invitation) and JOHN W. MEHL, *Dept. of Biochemistry, Univ. of Southern California School of Medicine*. A material corresponding to a mucolipoprotein has been isolated from normal human plasma. It appears to be identical with the material responsible for the polarographic cancer test (Acta radiol. et cancerol. bohém. et morav. 2: 27 (1939)), for the index of polypeptidemia (Biochem. Zeit. 121: 262 (1921)), with blood proteose (J. Natl. Cancer Inst. 4: 417 (1944)), and with seromucoid (Biochem. J. 34: 931 (1940)). The material is soluble in sulfosalicylic acid or perchloric acid, but not in tungstic acid or optimal concentrations of trichloroacetic acid. It is heat stable, and is precipitated by saturated ammonium sulfate and by 60 per cent ethyl alcohol.

Isolation was from perchloric acid filtrates of plasma by saturating the dialyzed filtrate with ammonium sulfate and lyophilizing the precipitate after removing the salts by dialysis. The isolated material was studied using electrophoretic methods and was found to contain at least three components, two of which accounted for 90% of the total.

The material contained 7.6 per cent nitrogen, 16.4 per cent galactose, 17.9 per cent hexosamine, and 20 per cent lipid. It was 58 per cent protein as measured by a quantitative biuret test and was found to be highly antigenic in rabbits. The molecular weight, amino acid composition, and physiological significance of the material are being investigated.

Colorimetric determination of  $\beta$ -diketones and triacetic lactone (6-methyl pyranone). ROBERT F. WITTER (by invitation) and ELMER STOTZ, *N. Y. State Agric. Expt. Sta., Cornell Univ., Geneva, N. Y.* In order to study the possible role of the  $C_6$  diketo acids and esters in the metabolism of fats, it was necessary to have methods for their determination.

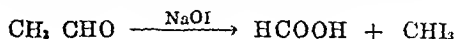
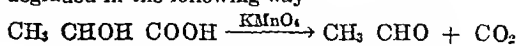
Acetylacetone, ethyl triacetate, or triacetic acid react with *o*-phenylenediamine to form the purplish red dimethylbenzodiazapine. This reaction has been placed on a quantitative basis for the measurement of 1 to 8  $\mu M$  of these diketones using acetylacetone as a standard. The full color develops within 30 minutes at pH 1.3-2.0 in the presence of an excess of *o*-phenylenediamine. Triacetic lactone does not react directly, but it may be converted by acid hydrolysis to acetylacetone, which is separated by distillation.

These compounds have been successfully recovered from metaphosphoric acid filtrates of bacteria and fungi cultures, kidney homogenates, and urine. Limiting concentrations of interfering compounds have been determined. Crotonaldehyde, when present in 5 to 10 times the quantity of acetylacetone, interferes, but this can be eliminated by the addition of small amounts of bisulfite after color development.

Photosynthesis with  $C^{14}O_2$  and the distribution of heavy carbon in the sugars. HARLAND G. WOOD and GEORGE O. BURR, *Dept. of Biochemistry, Western Reserve Univ., Cleveland, Experiment Station, H S P 4, Honolulu*. The purpose of the experiments was to determine the relative rates of assimilation of carbon dioxide in sugars and the distribution of the assimilated carbon within the sugar molecule during photosynthesis by bean plants.

Plants approximately three weeks old were exposed for  $\frac{1}{2}$  hour to carbon dioxide labelled with  $C^{13}$ . The sugars of the plants were then obtained in three fractionations by alcohol extraction, first 80 per cent, then 10 per cent, and finally 10 per cent after hydrolysis with saliva. The 80 per cent soluble fraction was further fractionated by fermentation with *Lactobacillus casei* and the lactic acid (L1) was separated. The non fermentable sugar was then hydrolyzed with acid and fermented to lactic acid (L2). Likewise after acid hydrolysis the 10 per cent soluble (L3) and saliva hydrolyzable portions were fermented (L4). These fractions are believed to contain predominantly carbon from the following sugars, L1 glucose, L2 sucrose, L3 dextrin, L4 starch.

These four lactic acid fractions were chemically degraded in the following way:



The  $\text{CO}_2$ ,  $\text{HCOOH}$  and  $\text{CHI}_3$  contain carbons 3 and 4, 2 and 5, 1 and 6 respectively of the hexose sugars

It has been found that the  $\text{CO}_2$ ,  $\text{HCOOH}$  and  $\text{CHI}_3$  from the L2-sucrose fraction contained a higher concentration and far more  $\text{C}^{13}$  than did any of the other fractions. However when the exposure to  $\text{C}^{13}\text{O}_2$  was three days, instead of  $\frac{1}{2}$  hour, the  $\text{C}^{13}$  was approximately equally concentrated in all four lactic acid fractions

There was some variation in the  $\text{C}^{13}$  concentration between the  $\text{CO}_2$ , formic acid, and  $\text{CHI}_3$ . However the reliability of these results is not fully established

The results indicate that  $\text{CO}_2$  is converted most rapidly to sucrose. Additional investigations are being conducted to more rigorously identify the sucrose and establish its  $\text{C}^{13}$  content

One blood sample per rabbit per test day in the assay of insulin D M YOUNG and R G ROMANS (introduced by E W McHenry) *Connaught Medical Research Labs, Univ of Toronto* Experience gained from the performance of one hundred and two twelve-rabbit insulin assays is described. In carrying out these assays, insulin was injected intravenously and one sample of blood for glucose analysis was drawn from each rabbit on each test day. The single blood samples were drawn 50 minutes after the injection of insulin. No significant variation in the slope of the dosage-response curve was detected over a 14 month period. Significant variations did occur in the estimated variance for error. The standard error of a twelve-rabbit assay of the type described was found to be of the order of 11 or 12 per cent

## THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

THIRTY-SEVENTH ANNUAL MEETING

Chicago, Ill, May 18, 19, 20, 21, 22, 1947

(For possible corrections in any of the following abstracts see the next issue)

Preliminary observations on the influence of ergotamine and dihydroergotamine on cerebral blood flow in the dog<sup>1</sup> BENEDICT E ABREU, GRANT W LIDDLE (by invitation), CARROLL A HANDLEY and HENRY W ELLIOTT (by invitation) *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco, and Dept of Physiology and Pharmacology, Baylor Univ College of Medicine, Houston, Texas* Until the recent introduction of the Kety and Schmidt  $\text{N}_2\text{O}$  method for determining cerebral blood flow (*Am J Physiol* 143: 53, 1945), there was no adequate method for studies in the intact animal

Preliminary studies employing this method have been made on the intact dog anesthetized with sodium pentobarbital, 25 mg/kg, I/P. Simultaneous venous and arterial samples were obtained at 2, 4, 6, and 10 minutes from the start of inhalation of  $\text{N}_2\text{O}-\text{O}_2$  mixtures (40%  $\text{N}_2\text{O}$  and 60%  $\text{O}_2$ ). Venous blood was obtained from the region of the torcular microphili and arterial blood from the femoral artery. Blood pressure was measured at intervals by means of the Hamilton manometer. Blood samples were analyzed for  $\text{N}_2\text{O}$  by the Orcutt and Waters procedure (*J Biol Chem* 117: 509, 1937)

Ergotamine tartrate, 0.05 mg/kg, I/V, 10 to 20 minutes prior to blood flow determination did not significantly alter blood pressure, but produced

elevations in cerebral blood flow varying from 16% to 83% of the control. Likewise, dihydroergotamine,<sup>2</sup> 0.1 mg/kg I/V, 20 minutes prior to blood flow determination had no appreciable effect on blood pressure, and increased cerebral blood flow by amounts varying from 102% to 136% of control

Antagonism of histamine with synthetic compounds which exert marked epinephrine-blocking effects. PAUL ACHENBACH (by invitation) and EARL R LOEW *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12, Illinois* Histamine antagonism and sympatholytic action were exerted by certain alkyl derivatives of  $\alpha$ -naphthyl-methyl- $\beta$ -chloroethylamine and 2-biphenoxyethyl- $\beta$ -chloroethylamine. Small oral doses in mice reduced the toxicity of epinephrine injected intraperitoneally. In anesthetized dogs, intravenous doses of 5.0 mg per kg completely reversed the pressor action of epinephrine. These compounds produced inflammatory reactions at the site of subcutaneous injection

A pronounced antagonism of histamine was exerted by  $\alpha$ -naphthylmethyl-ethyl- $\beta$ -chloroethylamine HCl, since subcutaneous injection of 0.025 to 0.1 mg per kg prevented or alleviated the symptoms of histamine shock and anaphylactic shock in guinea pigs. Antagonism of histamine was rapidly in onset and markedly prolonged. In dogs, the depressor effect of histamine was diminished or annulled

<sup>1</sup> Aided by a grant from the National Institute of Health, Bethesda, Md

<sup>2</sup> Supplied through the kindness of the Sandoz Chemical Works, New York, N Y



It is important to consider that such strong anti-anaphylactic activity was exerted by a compound which antagonized histamine and reversed the pressor action of epinephrine. It contrasts with other potent antihistamine and anti-anaphylactic drugs (Antergan, Necoantergan, Benadryl, Pyribenzamine and Antistin), all of which enhance the pressor response to epinephrine in animals. Therefore, this naphthyl derivative constitutes a pharmacological tool which should prove useful in determining whether the effectiveness of antihistamine drugs in diminishing or preventing anaphylactic and allergic reactions is importantly related to "epinephrine potentiation."

In each series of compounds studied, the higher alkyl derivatives exerted marked epinephrine-blocking activity but no appreciable antagonism of histamine, whereas the lower alkyl derivatives exerted both types of activity. The fact that both epinephrine and histamine were antagonized suggests that effects of other amines and bases may be blocked by these or closely related compounds [Compounds and financial support from Parke, Davis and Company].

Some effects of dibenamine on the mammalian heart. G. H. ACHESON, ALFRED FARAH (by invitation), and GORDON N. FRENCH (by invitation). *Dept. of Pharmacology, Harvard Medical School, Boston*. The accelerator effect of epinephrine on the acutely denervated heart of the cat or dog is not diminished by dibenamine (dibenzyl  $\beta$ -chloroethylamine hydrochloride) in doses of 10 mg per kg. In the spinal cat 1 mg per kg considerably lessens the pressor response to epinephrine. In the heart lung preparation of the dog (weight about 1 kg) as much as 150 mg of dibenamine diminishes neither the cardioaccelerator nor the positive inotropic effect of epinephrine. The same is true in the isolated rabbit auricle with 1 to 15,000 dibenamine. Yet in the isolated rabbit uterus, 1 to 15 million dibenamine depresses the contractions produced by epinephrine. It is concluded that with respect to sinus rate and inotropic effect the heart is resistant to the antiepinephrine effects of dibenamine as it is to those of 933F and ergotamine.

Large doses of dibenamine have a negative inotropic effect in the heart lung preparation and the rabbit auricle. In the latter preparation with concentrations of 1 to 100,000 or more, a gradual fall of sinus rate is seen, the electrical excitability (as measured after the relatively refractory period) is not significantly affected, but the maximal rate at which the auricle will follow an electrical stimulus is gradually lowered.

Influence of drugs, and uterine activity upon uterine blood flow. RAYMOND P. AHLQUIST and R. A. WOODBURY. *Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta, Georgia*. The blood flow in any muscular structure is influ-

enced both by active vasomotor changes and by passive effects of muscle activity. The blood flow was measured directly in one uterine artery by means of an optically recording rotameter in anesthetized, heparinized pregnant or post-partum dogs. The activity of the uterus was recorded simultaneously by means of balloons placed in one or both uterine horns. Arterial pressure was recorded from the inflow side of the flowmeter.

The blood flow was diminished by each uterine contraction. The greater the contraction, as measured by higher intra uterine balloon pressures, the greater the diminution of blood flow. When the intra uterine balloon pressure approached 60 to 70 mm Hg the blood flow practically ceased even though the mean arterial pressure was above 100 mm Hg. While high pressures were not obtained in the pregnant uterus a marked decrease in flow occurred with each contraction. For example, a contraction which increased the intra uterine pressure by 10 mm Hg produced a 25% decrease in blood flow. The blood flow in each uterine artery of the post partum dog was influenced almost entirely by the activity of the horn which it supplied. Contractions of the opposite horn had little effect on blood flow.

Drugs which produced active vasodilation include acetylcholine, histamine, atropine, magnesium, isopropyladrenalin and in pregnant uteri pitocin. Those which produced vasoconstriction include epinephrine, pitressin and in post partum uteri pitocin. [These studies were supported by financial grants from Eli Lilly and Company and U. S. Public Health Service].

Experimental studies on the use of starch as surgical dusting powder. SHANNON C. ALLEN and FLOYD D. LEES. *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Albany, California*. Several samples of starch powders provided by the Northern Regional Research Laboratory as possible substitutes for talc as surgical dusting powder were tested for suitability as powdering agents and compared for foreign body reactions with talc, potassium bitartrate and potassium acid saccharate. The latter was wholly unsuitable as a powdering agent but the starches compared favorably with talc and bitartrate and could be autoclaved successfully. All but one of 5 different starches were completely absorbed within 48 hours of intraperitoneal injection into young albino rats. After an initial inflammatory reaction three of these left the peritoneal cavity in completely normal condition even after ten weeks. The fourth, a formaldehyde treated cornstarch with a considerable residue of free HCHO, although absorbed, caused within ten days a characteristic and progressive foreign body reaction consisting of an almost complete encapsulation of the liver with thick ad-

hesions That this was due to the free HCHO was evident from the lack of such reaction when the starch was injected after thorough washing and from duplication of the reaction with injection of 0.5% HCHO either alone or as suspension medium for one of the innocuous starches The fifth, a commercial HCHO treated starch with no free HCHO, showed no apparent absorption after ten weeks and caused the formation of large granulomas and numerous adhesions

Evidence indicates that starch can be used successfully as surgical dusting powder but that its safety is determined by the type of processing it has undergone

**The protective action of rutin against capillary injury** ANTHONY M. AMBROSE and FLOYD DEEDS *Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Albany, California* Rutin has been reported to have beneficial actions on conditions of impaired capillary permeability or fragility The possibility of rutin protecting against capillary injury has been tested experimentally in rabbits using the accumulation of intravenously injected trypan blue into the irritated areas as a criterion of capillary damage Capillary injury was produced by means of chloroform, intracutaneous injection of histamine, and the application of negative pressure These procedures were applied to the depilated ventral surfaces of albino rabbits

Chloroform irritation was produced by the application for 30 seconds of a soaked cotton pledget Each rabbit received previously 2 ml of a 1% solution of trypan blue intravenously After control observations on the time of accumulation of dye into chloroform irritated areas, the rabbits received intravenously 1 ml/kg of a 20% solution of rutin in propylene glycol

In 22 rabbits, after the injection of rutin, the permeance of dye in newly formed chloroform wheals was delayed as much as 8 times over the control observations Intracutaneous injection of histamine before and after rutin administration gave some indications that rutin protected against the local action of histamine Five out of 6 rabbits to which negative pressure (30 mm of Hg) was applied for 1 minute showed blue stained wheals immediately after release of suction before rutin injection but none showed positive results when negative pressure was reapplied after rutin

It is concluded that rutin protects rabbits against capillary damage under the conditions of our experiments

**A compact and efficient apparatus of Pyrex glass for coronary perfusion** FREDERICK F. ANDERSON (by invitation) and BRADFORD N. CRAVER *Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey* The main portion of the apparatus

comprises an upper glass tube, 36 cm long and 7 cm in diameter, connected via a 45/50 glass joint to a lower double-walled glass chamber The warming coil in the upper tube passes down through the center of the joint, to which it is fused, to terminate in a double-walled lower chamber as a 3 cm vertical tube to which the heart can be attached To permit the injection of drugs a capillary passes through the outer wall of the tube to terminate in the warming coil just above the attachment of the heart The water in the upper tube is kept at constant temperature by a knife-type electric heater and thermo-regulator Circulation is maintained 1 By air bubbled into the bottom of the upper tube, 2 By three outlets, the first in the lower portion of the upper tube and connected by rubber tubing to the lower outlet of the double-walled chamber, the warmed water passes through the upper outlet of the latter to be returned through rubber tubing to the top of the upper tube Inserted into the middle of this last rubber tubing is a T-tube, through which air is bubbled to maintain the circulation The amount of perfusate dropping out of the S-tube on the bottom of the double-walled chamber is recorded by a flow meter and returned thence to the reservoir via an air operated automatic float The details of the two latter portions of the apparatus will, because of the limitations of space, be presented in slides

**Amebacidal and pharmacologic activities of the dithiocarbonylmethyl and dithiocarbonylphenyl derivatives of carbarsone oxide (p-carbamidophenylarsenous oxide)**<sup>1</sup> HAMILTON H. ANDERSON, EDER LINDSAY HANSEN (by invitation), PETER P. T. SAH and JOHN R. CAFISO (by invitation)<sup>2</sup> *Division of Pharmacology and Experimental Therapeutics, Univ. of California Medical School, San Francisco* The dithiocarbonylmethyl (1) and dithiocarbonylphenyl (2) derivatives of p-carbamidophenylarsenous oxide (3)<sup>3</sup> as well as the oxide exhibited amebacidal action *in vitro* within the range of emetine (1:20,000) Macaques naturally infected with *E. histolytica* were cleared for three months when given 25 mg/kg orally over ten days

The toxicity for mammalian tissues was lower for the dithiocarbonyl derivatives as shown by their action on rabbit's leucocytes and by comparison of their toxicity for small animals A dilution of 1/500 of (3) at 37°C caused morphologic changes within five minutes, but with the derivatives (1) and (2) there was no effect during the 30 minute test period

<sup>1</sup> The studies described in this report were made under contract, between the Office of the Surgeon General, United States Army and the University of California

<sup>2</sup> With the assistance of A. A. Stein, M. Dadmartz, Y. P. Chen and L. H. Ghessman

<sup>3</sup> Supplied by the Lilly Research Laboratories, Indianapolis, Indiana

LD <sub>50</sub>	Acute	(1)	(2)	(3)
Mice	I P	100 ± 18	265 ± 24	53 ± 13
Rats	I P	75 ± 11	76 ± 8	55 ± 4
Rats	I C	1000 ± 77	850 ± 200	510 ± 40

On short term intragastric toxicity tests (described by Carl C. Smith) (1) and (2) did not produce gross pathologic changes but growth was somewhat reduced (60% of controls) with (2).

Arsenic distribution studies have been made in rats, rabbits, and monkeys.

A method of studying ciliary motility by direct observation. WALTER E. BARRETT (introduced by Fredrick F. Yonkman) Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey. It was noted while using the carmine particle method that large accumulations of mucus interfered with the propulsion of the carmine and that subsequent removal of the mucus revealed the presence of active cilia. This led to varied results. Efforts were made to develop a technique which would allow one to observe the ciliary motility directly.

**Procedure.** Frogs were pithed and the esophagus and roof of the mouth were removed. These tissues were placed in a histological dish containing frog Ringer's solution. The esophagus was split longitudinally and pinned to a cork plate which was then anchored at the bottom of the dish.

From a section of the cork base which had previously been impregnated with paraffin, small hollow cork discs, 17 mm (outer diameter) by 5 mm (inner diameter) were cut out. A section of the esophagus which measured approximately 12 mm square was placed on the moistened cork disc and pinned to it by means of small sections of stainless steel wire.

The disc containing the specimen was placed on a microscopic slide which in turn was transferred to the microscope stage. Transmitted light was used to examine the esophageal mucosa. Examinations were made for the presence of active cilia before the tissues were placed in solutions of compounds under study. At the end of five minutes these specimens were removed to the microscope for re-examination of ciliary motility and then immediately returned to the test solutions.

The tissues were examined at five minute intervals for the first fifteen minutes and at ten to fifteen minute intervals thereafter for a total period of sixty minutes. Concomitant controls were studied in Ringer's solution.

**Discussion.** Since the nasal cavity will empty the mucus covering or blanket in thirty minutes (Proetz), a sixty minute period was established as the minimum time in which at least 50% of the cilia should remain active in any one concentration of a test compound.

Both the carmine particle and direct observation methods were used to study the effect of  $\beta$  phenoxethyl dimethyl dodecyl ammonium bromide upon frog ciliary activity. The highest concentration of PDDB<sup>1</sup> compatible with frog cilia for sixty minutes as determined by the carmine particle method was found to be 1:30,000, by the direct observation method a concentration of 1:10,000 concentration was compatible for sixty minutes. The reason for this discrepancy, therefore, is probably due to the accumulation of mucus which interfered with the propulsion of the carmine particles.

By the direct observation method, effective concentrations of an antibacterial compound could be studied for their compatibility with cilia.

The advantages of the direct observation method are twofold:

- (1) Ciliary activity is maintained for the required test period in higher concentrations of the drug than is revealed by the carmine particle method,
- (2) Several chambers can be handled together thus permitting simultaneous testing of varied concentrations of the drug.

**Toxicity of a new antiseptic ( $\beta$  phenoxethyl dimethyl dodecyl ammonium bromide) (PDDB).** WALTER E. BARRETT (by invitation), HARRY W. HAYS (by invitation), JAMES H. LEATHEM and ALICE A. GOODELL (by invitation) Research Division, Dept. of Pharmacology, Ciba Pharmaceutical Products, Inc., Summit, New Jersey. The LD<sub>50</sub> of  $\beta$  phenoxethyl dimethyl dodecyl ammonium bromide (PDDB)<sup>1</sup> has been determined in several species of laboratory animals and the results are summarized as follows:

- (a) Intravenous administration
  - Rats—18 mg/kg
  - Mice—31 mg/kg
  - Rabbits—11 to 12 mg/kg
- (b) Intraperitoneal administration
  - Rats—40 to 45 mg/kg
  - Guinea Pigs—10 to 20 mg/kg

In the cases of the intraperitoneal and oral routes of administration it was difficult to establish the LD<sub>50</sub>, since by the former route the resulting ascites and fluid shift masked the primary effect, while by the latter there was marked diarrhea with doses as high as 800 mg/kg and five of six survived.

This compound was also administered chronically for seven weeks to white rats of both sexes by gastric intubation. The dose employed was 10 mg/kg per day for five days a week. Although these animals showed some inability to gain weight as

<sup>1</sup> An abbreviation derived by combining the first letters of the component parts of the chemical name designed for convenience.

rapidly as litter mate controls they seemed quite normal and there were no significant changes in hematocrit values, red and white cell counts, or in the normal distribution of white cells

The cause for the slower weight gain in the treated rats is unknown, there was no change in bacterial flora of the gastrointestinal tract (Mayer & Lisman), alteration of which might have interfered with certain digestive processes, and there were no gross or microscopic changes in the following tissues: liver, kidney, adrenal, bone marrow, brain, heart, lung, spleen, thyroid, pituitary, ovaries, testis, pancreas, skeletal muscle and retina. Studies dealing with the effect of this antiseptic on digestive enzymes might shed some light on the problem of retarded weight gain, but from a practical point of view such studies do not appear urgent since oral administration of this agent in man seems contraindicated.

Earlier studies by W. Bosshard and L. Neipp who first studied this compound will soon become available (In press).

**The absorption of phenol in oily solutions by the rabbit skin.** A. BASS and S. C. WERCH *Medical Research Division, Plough, Inc., Memphis, Tennessee* (Introduced by C. C. Pfeiffer). A study was made of the absorption of oily solutions of phenol by itself or with camphor from uniform areas of rabbit skin.

In chronic experiments a solution of 4.6% phenol and 15% camphor in light mineral oil was applied daily for 14 days. Examination of urinary constituents, blood counts, total blood phenols, and organs revealed no abnormal changes.

Acute experiments were carried out with a special board permitting a fixed area of abdomen to be immersed in the test solution. Striking differences were found between the oily bases employed as regards total blood phenols and skin reactions. There was evidence that camphor may retard phenol absorption.

Mineral oil solutions of phenol or camphor or both caused hemorrhage and edema after short exposures. The oil itself caused no reaction. Vegetable oil bases produced at most a small amount of hemorrhage, without visible edema, only after long exposure and with high concentration of phenol.

A mineral oil solution of 1.6% phenol and 15% camphor gave lower blood phenol values than when camphor was omitted. Highest values were obtained with 4.6% phenol and 15% camphor. Vegetable oil solutions of 1.6% phenol, with or without camphor, gave the same phenol levels, whereas 1.6% phenol and 15% camphor solutions were not. However, the blood phenols were much lower when vegetable oils replaced mineral oil as solvents, the concentrations of phenol and camphor being the same.

**Effect of podophyllin on transplanted mouse tumors.** MORRIS BELKIN (introduced by R. P. Walton) *Dept. of Pharmacology, Medical College of South Carolina, Charleston*. King and Sullivan (Science, 104: 244-5, 1946) in treating condylomata acuminata with podophyllin noted cellular effects strikingly similar to those produced by colchicine. Since colchicine arrests tumor cell division in metaphase, it was considered of interest to test the action of podophyllin on transplanted mouse tumors.

Swiss mice carrying 15 day old implants of mouse sarcoma CR 180 were given subcutaneously podophyllin (U.S.P. X) dispersed in sesame oil in doses of 20 m.p.k. every 3-4 days for two weeks. At this time, tumor size in podophyllin treated mice, as expressed by their terminal volumes, was about  $\frac{1}{4}$  that of the controls. In a similar experiment, using a transplantable mammary adenocarcinoma in the C<sub>3</sub>H strain, the terminal volumes of the treated tumors were about  $\frac{1}{3}$  that of the controls.

For both types of tumors, the most prominent microscopic finding was extensive necrosis. Hydropic degeneration and vacuolization of the cytoplasm was more evident in CR 180 than in the mammary carcinoma. Characteristic nuclear changes were a diminution in number of mitoses, and pyknosis and karyorrhexis. Arrest of mitosis, usually at or before the metaphase, was a feature observed especially 24-48 hours after podophyllin administration.

In another series, in which mice carrying sarcoma CR 180 were sacrificed every 24 hours after a single dose of podophyllin, 20 m.p.k., these cellular changes were most striking 24 hours after administration of the drug, with recovery already apparent by 48 hours, well advanced by 72 hours, and practically complete after 96 hours.

**Tridione-diphenylhydantoin combination therapy in grand mal with slow-wave EEG dysrhythmia.** W. DEAN BELNAP (by invitation), JAMES E. P. TOMAN and LOUIS S. GOODMAN *Depts. of Physiology and Pharmacology, Univ. of Utah School of Medicine, Salt Lake City*. Since Tridione and diphenylhydantoin exhibit complementary anticonvulsant actions in laboratory tests (Goodman, Toman and Swinyard, *Am. J. Med.* 1: 213, 1946), they might be expected to show useful clinical synergism in grand mal. To test this assumption, seven consecutive patients (four to 21 years of age) with frequent grand mal seizures (one to 10 per month) and spontaneous inter-seizure slow-wave EEG dysrhythmia (not petit mal in type) were selected for trial with a combination of diphenylhydantoin (0.2 to 0.3 gram/day) and Tridione (0.4 to 1.2 gram/day). Initial slow-wave EEG dysrhythmia was focal in two cases, bilaterally symmetrical frontal in three, and

diffuse in two. Prompt and complete clinical remissions (one to nine months at present) were obtained in six patients, in two of whom previous phenobarbital diphenylhydantoin treatment had proved ineffective. In the seventh patient, seizures disappeared upon addition of phenobarbital (0.2 gram/day). Of six patients retested, the EEG returned to normal in four and was improved in two. No hematological or visual disturbances were observed, sedation occurred only in the patient receiving added phenobarbital. These preliminary findings appear to justify more extensive clinical trial of Tridione diphenylhydantoin, in place of the conventional phenobarbital diphenylhydantoin therapy, in young patients with grand mal associated with interseizure slow-wave EEG dysrhythmia. [Assisted by grants in aid of research from the U. S. Public Health Service, Abbott Laboratories and the University of Utah School of Medicine Research Fund.]

A study of the effect of digitoxin on blood oxygen. BYRL D. BENTON (by invitation) and W. J. R. CAMP, *Dept. of Pharmacology, Univ. of Illinois College of Medicine, Chicago 12*. Thirty-two dogs under pentobarbital anesthesia were used to determine the influence of decreased available oxygen on the action of digitals.

Six control experiments were done to determine the effects of anesthesia on the oxygen tension and capacity of arterial and venous blood. Eight additional dogs received 50 micrograms/kg. of digitoxin intravenously one hour after the anesthetic.

A severe anemia was produced in nine dogs, six receiving digitoxin, by bleeding from the femoral artery. The plasma with sufficient normal saline to restore the fluid volume withdrawn was returned.

To nine animals, six receiving digitoxin, 10 cc/kg. of CO was given by inhalation one hour after anesthesia.

Blood gases were determined by the Van Slyke manometric method, specific gravity by the falling drop method.

Results. In the control group arterial oxygen tension and specific gravity increased, the digitoxin dogs exhibiting slightly higher levels, and their venous oxygen tension remained lower longer. Following hemorrhage, arterial oxygen tension, oxygen capacity, and specific gravity decreased. Digitoxin dogs showed a less definite compensatory arterial increase and a pronounced fall in venous oxygen tension. After CO a more marked rise in arterial oxygen tension and capacity, and a more prolonged decrease in venous oxygen tension occurred in digitoxin dogs.

These results indicate an increased tissue utilization of oxygen, and an increased number of circulating red cells after digitoxin. The salutary effects of digitoxin when tissues suffer from anoxia may be

ascribed, at least in part, to an effecting of an increased utilization of oxygen by the cells.

The antithyroid activity of some 6-substituted-2-thiouracils. A. J. BERGMANN (by invitation), S. ANCHER (by invitation), J. O. HOPPE (by invitation) and T. J. BECKER, *Sterling Winthrop Research Inst., Rensselaer, N. Y.* Assays have been carried out on twelve new 6-substituted 2-thiouracils by the Astwood technique. The compounds were fed for ten days to young male rats at dietary concentrations of 0.001, 0.01 and 0.1%. Thiouracil was fed to control rats as the standard of reference. The results, based on the increase in weight and the reduction of the iodine content of the thyroids, indicate that two compounds of the series, cyclohexylmethylthiouracil and cyclopropylthiouracil are approximately five and ten times, respectively, as active as thiouracil.

Determinations were made of the basal metabolic rates of rats fed thiouracil or cyclopropylthiouracil for three weeks at dietary concentrations varying from 0.01 to 0.5%. Both compounds depressed the metabolism, cyclopropylthiouracil being the more active.

The acute, subacute and chronic oral toxicities of cyclohexylmethylthiouracil and cyclopropylthiouracil have been determined.

Neosynephrine bradycardia. BETTY L. BERTCHER (by invitation) and W. J. R. CAMP, *Dept. of Pharmacology, Univ. of Illinois College of Medicine, Chicago 12*. Neosynephrine HCl (20-40 micrograms/kg.) injected intravenously into dogs under pentobarbital anesthesia regularly effects a bradycardia as found in the ECG after the blood pressure peak has occurred. Equipressor doses of epinephrine effect a less marked change. After a sensitizing dose of physostigmine, the neosynephrine effect is more marked, one animal developing heart block and showing retrograde conduction. A less marked but definite effect is noted after bilateral vagotomy. After complete atropinization, neosynephrine produces bradycardia in 50 per cent of the experiments, while epinephrine has no such effect.

The site of action of neosynephrine appears to be both central and peripheral. That there is a definite central effect can be seen by the percentage decrease in bradycardia after vagal section. Whether it is a direct stimulation of the vagal center or carotid sinus cannot be determined from these experiments. That a neosynephrine slowing is obtained after vagal section is evidence of a peripheral action, predominantly a depression of the S-A node while a direct effect on the myocardium is indicated by the slowing obtained after atropinization.

The effect of caronamide on the renal tubular transport mechanisms for penicillin and other agents. KARL H. BEYER, A. KATHERINE MILLER

(by invitation), HORACE F. RUSSO (by invitation) and ELIZABETH K. TILLSON (by invitation, *Depts of Pharmacology and Bacteriology, The Medical Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* It has been found that 4'-carboxyphenylmethanesulfonamide, caronamide, completely and reversibly inhibited the tubular excretion of the various penicillins without inhibiting the renal transport mechanisms for glucose, amino acids, urea or sulfonamide reabsorption, glomerular filtration or ammonia formation. It was effective when administered orally or parenterally and when penicillin was administered by the same or a different route.

The competitive inhibition by caronamide of the transport mechanism for the tubular excretion of penicillin and *p*-aminohippurate is fundamentally different from the inhibition of penicillin excretion by "mass action" competition between *p*-aminohippurate and the antibiotic agent for excretion by the same tubular mechanism. The rate of elimination of caronamide is equivalent to the rate of glomerular filtration of mannitol.

**Chemotherapy of cotton rat filariasis with certain antimony and arsenic compounds.** RAYMOND N. BILTZER, ASHTON C. CUCKLER (by invitation), JOHN T. LITCHFIELD, JR., THERESA E. BREY (by invitation), and HAROLD N. WRIGHT, *Dept of Pharmacology, Univ of Minnesota Medical School, Minneapolis, Minnesota.* A comparative study has been made of the chemotherapeutic activity of nine organic antimonials, three arsenical compounds, and one combined antimonial arsenical derivative.

The compounds were tested (a) against the microfilariae, and (b) adult filaria in vitro and (c) against the adult filaria in vivo in *Litomosoides carini* infestations in cotton rats. Little or no correlation was found between either of the in vitro tests and chemotherapeutic effect in the intact animal, probably because of the necessity for the development of activity by metabolic changes after administration by several of the compounds.

The chemotherapeutic effects in *Litomosoides carini* infestations in cotton rats were determined by intraperitoneal injection of the compounds mostly at eight hour intervals for 18 or 36 injections with autopsy 36-48 hours after the last injection when the filariae were removed and placed in a modified Simm's solution. Evidence of chemotherapeutic activity was determined by the percentage of dead filaria found 24 hours after autopsy.

Considerable chemotherapeutic activity was evidenced when neostibosan was administered 18 or 36 times in doses of 60 mg/kg when anthiomaline was administered 36 times in doses of 12 mg/kg, when tryparsamide or melarsen were given in 18 doses of 100 mg/kg, and when an antimony deriva-

tive of sulfarsphenamine was given in 18 doses of 5 mg/kg [Work done under contract with the Office of Scientific Research and Development and the University of Minnesota. Grateful appreciation is accorded to Dr. Harry Eagle, Merck and Company, Parke, Davis and Company, Squibb, Wallace Laboratories, and Winthrop Chemical Company for supplying these compounds through the Chemotherapy Center].

**The effect of peritoneal irrigation on methyl alcohol toxicity.** W. S. BLAKEMORE and C. H. HINE (introduced by P. K. Smith). *National Naval Medical Center, Naval Medical Research Inst., Pharmacology and Toxicology Facility.* The MLD 50 and 95 of methanol was determined for adult white rats. Animals receiving 36 cc per kilogram of 50 per cent methanol by gavage (MLD 95) were treated by peritoneal irrigations using Tyrode's solution as described by Seligman, et al, for the treatment of uremia in acute renal failure. Nine out of 13 rats treated in this manner survived. Analysis for methanol using the method of Hine, et al, showed an average level of 3.7 mg of methanol per gram of brain in the treated animals and 8.5 mg per gram in the untreated series which were killed at the end of a 36-hour period. Analysis of the collected peritoneal washings showed that 30-70 per cent of the orally administered methanol could be recovered during an eight-hour period. The concentration of methanol in the peritoneal washings varied from 1100 mg to 20 mg per hour decreasing progressively every hour until the sixth hour at which time a relatively constant level was reached. Preliminary observations showed little correlation between the total recovery of alcohol and the rate of perfusion. Animals perfused without receiving methanol showed an insignificant amount of any oxidizable material that would have given false reading for methanol. With careful post-operative care animals can be protected from lethal doses of methanol by means of peritoneal irrigation.

**A collaborative study of methods for assaying analgesic drugs.** C. I. BLISS and ELMER L. SEVINGHAUS (by invitation). *Connecticut Agricultural Experiment Station and Scientific Dept., Hoffmann-La Roche, Inc., Nutley, N. J.* In the search for new analgesics different methods for testing analgesic potency are continually being offered in the literature. A group of investigators from universities and industry have undertaken a joint study to compare five compounds, morphine sulfate, codeine sulfate, demerol hydrochloride, amidone and aminopyrine, by various analgesic methods. The drugs were injected intraperitoneally at three different dosage levels and the response determined in each case. Each investigator followed the technique commonly used in his laboratory. In most cases this was a modification of the original Wolff-Hardy method in which the painful stimulus

is produced by radiant heat. The data have been analyzed statistically to compare the relative precision of the several methods and the agreement in relative potency of the five drugs.

Further observations on the effect of prolonged pentothal on metabolism of carbohydrates and of proteins. WALTER M. BOOKER, DAVID M. FRENCH, and PEDRO A. MOLANO (introduced by A. H. Maloney) *Dept. of Pharmacology, Howard Univ. School of Medicine*. Changes in the blood sugar level and in liver glycogen during prolonged pentothal anesthesia have been previously reported. Further observations are reported here in which animals on normal, high carbohydrate and high protein diets are compared as to their ability to dispose of pentothal sodium. The evidence suggests that animals on high protein diets dispose of pentothal more rapidly than animals on high carbohydrate or normal diets, since greater quantities of pentothal are required to maintain surgical anesthesia (3-4 hours) in animals on high protein diets than are required by animals on high carbohydrate or on normal diets. High protein diets, however, do not prevent the hyperglycemia that occurs during prolonged pentothal anesthesia. The hyperglycemia can be controlled by insulin if given along with or immediately following the administration of pentothal. Insulin appears not to increase the mechanism of disposing of pentothal, but it facilitates greater storage of glycogen of animals on normal diets. Insulin, however, does not significantly raise proportionately the liver glycogen in animals when glucose is administered during prolonged anesthesia.

Experiments show further that intermediary metabolism of carbohydrates and of proteins is disturbed as indicated by elevated blood lactates and decreased total NPN, and constituent substances.

**Depression of the thyroid gland by sulfathiazole, the effects on the pancreas.** WALTER M. BOOKER, HAMILTON PERKINS and ALVIN BLOUNT (introduced by A. H. Maloney) *Dept. of Pharmacology, Howard Univ. School of Medicine*. The MacKenzie, Astwood and others have shown how certain sulfonamides (particularly sulfaguanidine), thiourea and thiouracil, depress the thyroid gland. The present authors have been interested in re-investigating this work, concentrating their attention on sulfathiazole, to determine the extent of the thyroid depression as evidenced by growth curves and by histological study, and to determine what effect the thyroid depression might have on the pancreas in view of the probable thyroid-pancreas relationship. Growing rabbits (900-1200 grams) were divided into groups in order to receive the following combinations of drugs: 1) Sulfathiazole, (0.5 gram daily), 2) Sulfathiazole and desiccated thyroid (.5 gram and 0.12 gram respectively), 3)

Desiccated thyroid (0.12 gram daily) and insulin (2 units every other day), and 4) Sulfathiazole-thyroid (desiccated)-insulin, as outlined above. Experiments covered 4 to 8 week periods. Marked depression in growth existed in the sulfathiazole group, followed by the thyroid-sulfathiazole group, which during the first two weeks grew rapidly. The thyroid-insulin group showed at first a depression of growth, followed by a rapid recovery to compare favorably with the growth of the untreated controls. The insulin group showed a growth rate equal to and in some instances greater than the controls. Insulin injected into the sulfathiazole-thyroid group did not significantly change the pattern of growth. Decrease in the weight of the pancreas in the sulfathiazole treated animals are described. Variations of increase and decrease in pancreatic weights are described in animals on sulfathiazole thyroid combination. Blood sugar and histological changes in the pancreas are under investigation.

**The inhibition of the cholinesterase activity of human and canine blood plasma and erythrocytes by certain phosphate esters.** RALPH W. BRAUER (by invitation), HAROLD C. HODGE, and HERBERT A. RAVIN (by invitation) *Dept. of Pharmacology, Harvard Medical School, and Dept. of Pharmacology and Toxicology, School of Medicine and Dentistry, The Univ. of Rochester, Rochester, New York*. A number of phosphate esters have been found to be potent inhibitors of the cholinesterase activity of human and of canine blood plasma and erythrocytes. The most potent of the compounds tested was hexaethyl tetraphosphate (tri diethyl phosphophosphate) which, *in vitro* on a molar basis, is about one thousand times as active as di isopropyl fluorophosphate. All of the compounds tested lose their activity on standing in an aqueous solution, presumably due to hydrolysis to the much less active di- and trialkyl phosphates. The inhibition of the cholinesterase activity of neither erythrocytes nor of blood plasma can be reversed by dialysis for twenty four hours against 0.9% aqueous sodium chloride solution, or against normal dog plasma. Higher concentrations of these inhibitors were required to produce the same degree of inhibition of the cholinesterase activity of erythrocyte suspensions than of plasma esterase dilutions of comparable activities.

The intravenous administration of hexaethyl tetraphosphate to dogs in doses sufficient to reduce the plasma esterase activity of these animals to about ten per cent of the basal level did not result in any appreciable physiological response. Recovery of the original esterase level is accomplished in seven to ten days.

**A comparative study of the intravenous cat and intravenous pigeon methods for digitalis assay.** H. A. BRAUN and L. M. LUSKY (by invitation)



*Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25,* D C While the U S P XII intravenous cat method for digitalis assay has been generally satisfactory, the cost of cats is becoming a considerable item Investigation of the intravenous pigeon method indicates that comparable results can be obtained at a considerable saving in cost Digitalis dilutions were infused into the alar vein at a rate and concentration to cause death in pigeons in 60 to 90 minutes

Assays by both methods have been completed on a considerable number of digitalis preparations (powders, tinctures, capsules, tablets, pills, and powdered extract) The potencies by the two methods have agreed within  $\pm 10\%$  Generally 6 to 8 pigeons each are required for the standard and unknown in order to reach the standard error of  $\pm 5.7\%$  required by the U S P XII

**The hot wire anemometer as a flowmeter** H D BRUNER *Dept of Pharmacology, Univ of Pennsylvania, Philadelphia* The hot wire anemometer used by Machella (*Am J Physiol* 115 632, 1936) chiefly as a velocity meter was investigated as a flowmeter by incorporating the wire into fixed dimension plastic units through which an artificial circulation simulated the velocity pulses and flows encountered *in vivo* By use of a high capacity across a high sensitivity, long period galvanometer, the pulses were converted into a reasonably steady deflection which could be calibrated as flow per minute This was true, however, only so long as the temperature of the circulated liquid was constant It proved impossible suitably to compensate temperature variations either by a thermopile or by balancing the Kelvin bridge with a matching wire stretched in the relatively quiescent flow near the wall In common with other types of thermoelectric flowmeters designed for implantation intravascularly, the sensitivity of the blood to temperatures above  $45^{\circ}\text{C}$  limits heating the element above that temperature under the existing conditions of flow As a result small changes in temperature of the liquid modify the gradient of heat transfer under otherwise constant conditions and direct calibration values no longer apply Since at least five determinants of heat transfer (liquid temperature, flow, contours and rate of velocity pulses, specific heat of the liquid, insulation of the wire by adhering platelets and fibrin) may vary unpredictably over several hours, the system was considered unsatisfactory for long term *in vivo* blood flow measurements

**Circulation time through the kidney** H D BRUNER, JOHN K CLARK (by invitation) and HAROLD G BARKER (by invitation) *Dept of Pharmacology, Univ of Pennsylvania, Philadelphia* The renal circulation time was studied by intra arterial injection of the dye T 1824 and

radioactive phosphorus while the blood flow was being measured by bubble-meter in eviscerated rabbits and dogs Curves of the return of  $\text{P}^{32}$  in the vein were followed by a suitably shielded Geiger-Muller tube whose impulses were registered on the ammeter of an integrating counting-rate meter, the ammeter and a high speed clock were photographed at eight frames per second and the data plotted The graphs indicate renal vascular circuits of varying length and/or varying velocity flows The dye circulation time gives only the minimal circulation time, although the renal vein blood continues dark for many more seconds, also the interval so measured depends on perception of threshold discoloration of blood The results invalidate use of the dye circulation time of the kidney as objective physiologic evidence of shunt circuits in the kidney

**Tolerance of excised muscle for sodium sulfadiazine, with prolongation of survival by certain concentrations** E H BRUNQUIST, BERTIE WARREN and CURUS W PARTINGTON (introduced by Richard W Whitehead) *Dept of Physiology and Pharmacology, Univ of Colo School of Medicine, Denver* Excised sartorius muscles of small frogs were fixed in a moderately extended position in Ringer's fluid or in Ringer's fluid plus the drug

The tolerance of the excised muscle was determined for concentrations of sodium sulfadiazine much greater than the blood concentration which is achieved in connection with the therapeutic use of the drug In acute experiments, reactivity of muscle to faradic shocks was abolished in from 100 to 220 minutes ( $13^{\circ}$  to  $14^{\circ}\text{C}$ ) by concentrations varying from 4% to 5%, but excitability returned when the tissues were returned to Ringer's fluid, with subsequent survival for from 9 to 21 days

In other experiments, one muscle of each pair from a frog was kept continuously in a 0.4% solution of the drug in Ringer's fluid, while the other one served as a control in unmodified Ringer's Presence of the drug in this concentration in the immersion fluid almost invariably prolonged the period of survival of excitability in the tissue, both at  $13^{\circ}$  to  $14^{\circ}\text{C}$  and at  $25^{\circ}\text{C}$  For example, in the case of 19 pairs of muscles maintained at the lower of these temperature levels, the average survival time of the controls was 21 days, and that of the experimental muscles  $34\frac{1}{2}$  days

**Effect of cyanine dyes and of sodium fluoroacetate on the metabolism of filariae (*L. carini*)** ERNEST BLEDINE *Dept of Pharmacology, School of Medicine, Western Reserve Univ, Cleveland, Ohio* In concentrations varying from  $1 \times 10^{-7}$  M to  $4 \times 10^{-7}$  M, certain cyanine dyes, such as 1'-ethyl-3,6-dimethyl-2-phenyl-4-pyrimido-2'-cyanine chloride, inhibit the oxidative metabolism of the filarial worm, *L. carini* Only in concentrations 1000 to 2000 times higher are the oxygen

uptake of mammalian tissues (slices of homogenates) and the activity of cytochrome oxidase and of cytochrome C decreased. The inhibition of the respiratory metabolism of filariae produced by the cyanines is associated with an increase in aerobic glycolysis. After the intraperitoneal administration of very small doses of cyanines (0.1 mg per kg daily for 5 days) to cotton rats infected with filariae, respiration of the worms removed from these animals is decreased, while their rate of glycolysis is increased. Since the administration of 2 to 4 times higher doses results in the death of the filariae, the curative action of the cyanines on the filariasis of the cotton rat is probably due to the inhibitory effect of these compounds on the respiratory metabolism of the parasite.

The aerobic utilization of glucose by filarial worms is much greater than that of lactate or of pyruvate. In the presence of fluoracetate the aerobic incubation of filariae with glucose results in an accumulation of pyruvate and the aerobic utilization of added pyruvate is completely inhibited. Detectable amounts of acetate are not formed from glucose or pyruvate either in the presence or absence of fluoracetate.

Some observations on the action of miracil (1-( $\beta$ -diethylaminoethylamino)-4-methylthioxanthone hydrochloride) against *Schistosoma mansoni*. ERNEST BUEHING, AEME HIGASHI (by invitation), LAWRENCE PETERS, and ARTHUR D. VALK. Dept of Pharmacology, School of Medicine, Western Reserve Univ., Cleveland, Ohio. The previously reported ability of this compound to exert a chemotherapeutic effect against *S. mansoni* was confirmed. In doses of 36 mg/kg, administered intraperitoneally every 8 hours for 18 doses, approximately 75% of treated mice survived. In half of the survivors no flukes could be found at autopsy in spite of the presence of severe schistosomal liver damage. In the remainder, flukes were recovered from the liver, but, in contrast to untreated controls, no flukes were found in the portal and mesenteric veins. Lower doses (e.g., 24 mg/kg) resulted in the same change in distribution of flukes, with no complete cures.

In all cases the surviving flukes of treated mice showed a decreased rate of glycolysis as compared to controls, but no change in  $Q_{O_2}$ . When added to flukes *in vitro*, miracil inhibited neither glycolysis nor respiration, suggesting the possibility of conversion, *in vivo*, to an active metabolite. However, the formation of a metabolite inhibiting glycolysis of schistosomes could not be demonstrated. Extraction of urine or carcasses of mice which had received miracil, yielded no product active *in vitro*. Incubation of drug with tissue slices (liver, diaphragm or both) failed to produce a demonstrable conversion to an active compound, even if schistosomes were present during incubation.

The possibility that some metabolic reaction other than glycolysis might be affected was also investigated to some extent with negative results. For example, no effect of miracil on metabolism of nucleoproteins or on proteolytic activity could be demonstrated.

Metabolism of schistosomes (*S. mansoni*). ERNEST BUEHING, LAWRENCE PETERS, and ARNOLD D. WEICH. Dept of Pharmacology, School of Medicine, Western Reserve Univ., Cleveland, Ohio. Cyanine dyes active in inhibiting the respiration of filarial worms, inhibit with equal effectiveness the oxidative metabolism of schistosomes. In contrast to the experience with filariae, inhibition of aerobic metabolism did not produce the death of schistosomes. When rabbits infested with *S. mansoni* were given repeated intravenous injections and infusions of a cyanine dye, the respiration of the schistosomes removed from the host was almost completely inhibited, but the parasites remained alive and motile. In schistosomes the rate of anaerobic glycolysis was almost as great as the rate of aerobic glycolysis, and the same proportion of the glucose utilized was converted to lactic acid under aerobic as under anaerobic conditions. Sodium Antimony III bisacatechol 2,4 disulfonate ('Fuadin') was more effective in depressing the respiration than the glycolysis of schistosomes. Search for effective inhibitors of the glycolysis of *S. mansoni in vitro* indicated that 2-methyl-1,4-naphthoquinone possesses considerable activity. When mice infested with schistosomes were fed a diet containing 1 to 1.5% of 2-methyl-1,4-naphthoquinone for one week and, during this period, were injected intraperitoneally with subcurative doses of 'Fuadin' (7.5 mg/kg every 8 hours for 5 days), the schistosomes removed from the livers of these mice exhibited a markedly decreased rate of glycolysis (60 to 90% inhibition). Furthermore, this dosage schedule resulted in the disappearance of the parasites from the mesenteric veins of the hosts. No chemotherapeutic effects were observed after the administration of similar amounts of either drug by itself. It is concluded that the synergistic effect of 2-methyl-1,4-naphthoquinone is due to its inhibition of glycolysis in schistosomes and that this metabolic reaction rather than respiration is essential for the survival of these organisms.

Metabolic fate of thiobarbital. MILTON T. BUSH and THOMAS C. BUTLER. Vanderbilt Univ. School of Medicine. Some of our previous studies have shown a correlation between the duration of action and the metabolic fate of certain barbituric acid anesthetics (N-methylbarbital, N-methyl phenobarbital). The present work was undertaken to answer the question: is the long duration of the hypnotic action of large doses of thiobarbital associated with the formation *in vivo* of the oxygen analogue of this substance, barbitol? Dose duration-

of-action studies in mice indicated that this reaction might occur

The urine of dogs given thiobarbital has been put through a procedure designed to isolate thiobarbital and barbital, involving the use of systematic multiple fractional extractions. We have failed to find either drug in the urine after administration intraperitoneally of 100 mg thiobarbital per kg to dogs.

The analytical results indicate that less than 5% of the thiobarbital was excreted unchanged, and that less than 15% was excreted in the form of barbital. It is expected that these upper limits can be set lower as the precision of the analytical technique is increased.

**Anti-enzymatic action of salicylates and related drugs, tested by new *in vitro* method.** B CALESNICK (by invitation) and R BEUTNER, *Dept of Pharmacology, Hahnemann Medical College, Philadelphia, Penna.* Repeating the work of F Guerra, we have found that the spreading of dyes (Trypan Blue and Evans Blue) by the simultaneous intra dermal injection of hyaluronidase into albino rabbits is inhibited to a marked degree if sodium salicylate is administered intravenously. It was further found that acetylsalicylic acid, orally, has a similar inhibitory effect. We also utilized a modification of the turbidity assay of hyaluronidase (Kass and Seastone). Our *in vivo* results were confirmed by this *in vitro* method. The procedure for this determination is as follows: A suitable concentrate of the enzyme solution (20 gamma/cc) was pipetted into test tubes to which was then added the buffer solution (pH 6.0). Sodium salicylate was then added and the tubes set aside at room temperature for 15 minutes. Then, the substrate (potassium hyaluronate) was added and the solutions incubated for 24 hours. Following this, another buffer (pH 4.2) was pipetted into these tubes with diluted normal horse serum. The enzyme substrate mixture was again incubated for 45 minutes and the turbidity observed grossly. Sodium salicylate showed a definite anti-enzymatic action against hyaluronidase. Several substances, chemically related to salicylic acid, have also been tried and thus far only parahydroxypropyl benzoate was found to possess a detectable hyaluronidase-inhibitory effect.

**Contributions to an elucidation of the pharmacological action of histamine.** ANNE CAMERON (by invitation) and BRADFORD N CRAVER, *Dept of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey.* By using dogs with Thiry-Vella loops in the manner to be described elsewhere, the following data were secured: (1) Physostigmine but not mechoyl definitely potentiated the action of histamine on the intestine, (2) calcium ions partially inhibited that action, (3) atropine usually inhibited the

action of histamine completely and that inhibition could be partially eliminated by physostigmine, (4) after the administration of antihistaminics and atropine-like compounds, histamine often gave a significant inhibition of motility which might or might not have been followed by secondary stimulation, that inhibition was shown, by the use of adrenalectomized dogs, not to have been due to epinephrine but probably to a stimulation of the sympathetic ganglia by histamine, (5) tetraethylammonium bromide overcame to some extent the antihistaminic activity of atropine, it was shown to cause intestinal stimulation which could be prevented by atropine, and also to paralyze partially the sympathetic ganglia. The data secured strongly support the previously advanced hypothesis that the pharmacological actions of histamine are mediated by the organism's endogenous acetylcholine.

**Specificity of the increased resistance induced in mice by streptococcal toxin.** G L CANTONI and A W BERNHEIMER (by invitation), *Dept of Pharmacology, Long Island College of Medicine, Brooklyn, New York and Dept of Bacteriology, New York Univ College of Medicine, New York, New York.* It was previously shown that a preliminary administration of a sublethal amount of preparations containing the oxygen-labile hemolysin of Group-A hemolytic streptococci induces a significant degree of protection against a lethal dose of the same preparation (A W Bernheimer and G L Cantoni, *Feder Proc* 5 No 1, 1946). To analyze the specificity of the refractory state, a variety of agents has been examined most of which are cardiotoxic as well as hemolytic and therefore have a pharmacological activity more or less resembling that of the streptococcal preparation.

Mice made refractory to streptococcal toxin exhibited normal susceptibility toward each of a series of other toxic agents. However an unexpected relationship was revealed when mice which had received a preliminary injection of a sublethal amount of streptococcal toxin, were injected with a lethal dose of saponin. Mice treated in this way exhibited a degree of refractoriness to saponin comparable to that which develops against streptococcal toxin. Similarly mice injected with a sublethal dose of saponin developed refractoriness to the effect of a lethal dose of saponin or to that of a lethal dose of streptococcal toxin. These observations are interpreted as pointing to a fundamental and hitherto unknown similarity in the pharmacological actions of streptococcal toxin and saponin. [Aided by grants from the John and Mary R Markle Foundation for Medical Research and the Life Insurance Medical Research Fund.]

**Acid soluble phosphorus compounds of heart muscle.** G L CANTONI, *Dept of Pharmacology, Long Island College of Medicine, Brooklyn, New*

*York* The acid-soluble phosphorus compounds of tissues have been the object of numerous investigations inasmuch as these compounds play a key role in carbohydrate and energy metabolism. When trichloroacetic acid extracts of skeletal muscle are fractionated into the different individual compounds (W. W. Umbreit, R. H. Burris and J. F. Stauffer, 1945. *Microanalytical Techniques* etc.) 95-100% of the total acid-soluble phosphorus is accounted for. Similar experiments performed using heart muscle revealed that a large fraction of organic phosphorus cannot be accounted for in terms of any of the well-known phosphorus compounds found in fresh tissues.

This unidentified fraction remains in the alcohol supernate after barium precipitation; it corresponds to 22-32% of the total acid-extractable phosphorus of frog's heart and to 9-18% of that of rabbit's heart. The unidentified phosphorus compound in this fraction is in all probability a single substance.

No precipitate forms from aqueous or alcoholic solutions with uranium, lead or silver acetate, mercuric chloride, and brucine sulphate.

Little or no orthophosphate is released by hydrolysis in 5 N HCl or NaOH. Oxidation by 0.09 N trisodium tetraperiodate followed by hydrolysis in 5 N acid at 100° converts quantitatively the organically bound phosphorus to orthophosphate. Choline was identified following acid hydrolysis but our data do not as yet permit evaluation of the ratio  $\frac{\text{bound choline}}{\text{organic phosphorus}}$ .

These and other results suggest that the unknown compound found in fresh heart muscle might be similar to or identical with alpha-glycerylphosphorylcholine which has been isolated from pancreas autolysates (G. Schmidt, B. Hershman and S. J. Thannhauser, *Jour. Biol. Chem.* 161: 523, 1945).

Experiments in progress aim at the isolation and purification of the compound from fresh beef heart.

The anesthetic properties of three isomeric ethers C. JELLEFF CARR, *Dept. of Pharmacology, School of Medicine, Univ. of Maryland*. In studies with three isomeric volatile aliphatic ethers, namely, diethyl ether, n-propyl methyl ether (Metopryl) and isopropyl methyl ether (Isopryl), it was found that physical properties play a predominant role in predicting anesthetic activity. Among the physical properties, water insolubility and oil/water coefficient are of paramount importance. The measurements of induction time in mice and the anesthetic index in the dog were capable of showing a difference between n-propyl methyl ether and diethyl ether. Clinically the increased anesthetic potency for Metopryl was manifested in more than 500 anesthetics, by noting the volume of agent employed compared with that

of diethyl ether. Blood levels of Metopryl during surgical anesthesia showed a range of 40 to 90 mg per cent. The value for diethyl ether is 110 to 140 mg per cent. Isopryl and diethyl ether are relatively close in potency and there is less significant correlation between physical properties and the biological data for these two ethers.

The excised guinea pig trachea in the study of anti-histamine drugs JULIO C. CASTILLO (by invitation) and EDWIN J. DE BLEER, *The Wellcome Research Labs., Tuckahoe 7, New York*. The excised guinea pig trachea has been found to exhibit good smooth muscle reactions similar to that of the bronchi, and to be a useful preparation for the study of anti-histamine drugs. The problem of magnifying the constrictions and dilations of the trachea when exposed to drugs has been solved in simple fashion by sectioning the entire trachea of a guinea pig into 12 rings of approximately the same width and connecting the rings in chain fashion with short loops of silk thread.

In the study of anti-histamine drugs, the tracheal chain responds to histamine with long sustained submaximal contractions which facilitate the qualitative and quantitative study of the ability of the antispasmodic to relieve a histamine spasm. Differences between a fast-acting and a slow-acting anti-histamine drug can be clearly demonstrated. In the screening of compounds for anti-histamine activity, the guinea pig trachea differentiates between a bronchodilator drug and a truly specific anti-histamine substance.

Preliminary results obtained indicate that the tracheal chain is suitable for quantitative work and a paper dealing with the use of this preparation for the assay of anti-histamine drugs is now in progress.

Antagonism of curare action by di-isopropyl-fluorophosphate (DFP) HAROLD F. CHASE, JOHN L. SCHWIDT (by invitation), and BANI K. BHATTACHARYA (by invitation), *Dept. of Pharmacology and Division of Anesthesia, of the Dept. of Surgery, School of Medicine, Western Reserve Univ. and Univ. Hospitals of Cleveland*. The effect of the cholinesterase inhibitor, di-isopropylfluorophosphate (DFP), on the curarizing activity of d-tubocurarine was studied by the rabbit head drop assay method for measuring curare activity. Groups of 7 to 14 rabbits were used in each assay. Comparisons of test with control data for the same animals were analyzed by statistical methods for correlated data.

Rabbits given prior injections of 0.2 and 0.3 mg of DFP per kg required 197 and 222 per cent, respectively, of the dose of d-tubocurarine needed to produce head drop with the curarizing drug alone. Three groups of 7 rabbits each were given 0.2 mg of DFP per kg intravenously. Titration with d-tubocurarine was started one minute later, five minutes later, and one hour later in the re-

spective groups. The head drop doses in all three groups were increased in approximately equivalent amounts (about 100 per cent) above control doses, suggesting that the antagonistic action of DFP, intravenously administered, occurs very rapidly and is maintained undiminished for at least one hour. The further duration of the effect of this single dose of DFP was studied by repeated assays with d-tubocurarine, in two groups (14 rabbits) of the animals mentioned above, on the first, second, third, fifth and twelfth day following the DFP injection. On the first day the head-drop doses were elevated about 50 per cent and on the fifth day about 20 per cent. On the twelfth day the dosage required was still 9 per cent above that of the control. A second injection of DFP (0.2 mg per kg) on the fourteenth day of the experiment caused a secondary rise of the curarizing dose to 57 per cent of the control value.

Mazur and Bodansky (J Biol Chem 163 261, 1946) have described, and illustrated in their second figure, the rate of regeneration of cholinesterase in plasma, in red blood cells, and in brain, following its inactivation by similar doses of DFP in rabbits. The recovery of normal response to curare following DFP resembles the rate and time sequence of regeneration of red blood cell cholinesterase.

**Certain pharmacologic effects of  $\beta$ -piperidinoethyl phenyl- $\alpha$ -thienylglycolate.** JAMES Y P CHEN (by invitation)<sup>1</sup> and BENEDICT E ABREU *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco*. In dogs, anesthetized with sodium pentobarbital,  $\beta$  piperidinoethyl phenyl- $\alpha$ -thienylglycolate HCl (PPT) 10 mg/kg, I V, decreased mean arterial pressure from 129 mm Hg (108-140) to 79 mm Hg (78-90) and increased mean cardiac rate from 62 (52-80) to 185 (140-225) per minute. Cardiovascular anti acetylcholine effects were produced by PPT, 0.5, 1.0, 5.0 and 10 mg/kg, I V. The mean duration of anti acetylcholine action with 10 mg/kg, I V, was 91 minutes (58-119). There was a mean decrease in the blood pressure response to histamine amounting to 26+ mm Hg (22-32) after 10 mg/kg, I V.

A comparison of this agent with benadryl  $\beta$  diethylaminoethyl and phenyl  $\alpha$ -thienylacetate (DPT) indicated that it is approximately twice as effective as benadryl and three times as effective as DPT in depressing the response to acetylcholine, and half as effective as benadryl and one and one-half times as effective as DPT in decreasing the response to histamine.

In unanesthetized monkeys, rabbits and mice

PPT produced clonic convulsions which progressed to tetanic convulsions as the dosage was increased. The subcutaneous tetanic convulsant dosage was 140 mg/kg for the rabbit and 90 mg/kg for the mouse. The I M tetanic convulsant dosage for the monkey was 56 mg/kg. Convulsions in monkeys were abolished by ether anesthesia.

Chronic subcutaneous administration of PPT, 40 mg/kg daily, and DPT, 80 mg/kg daily, to rabbits for 42 days resulted in anorexia, loss of body weight, slight impairment of renal but not hepatic function, slight granulocytopenia and an increase in hemoglobin concentration, erythrocyte and leucocyte counts. [Aided by a grant from Frederick Stearns & Company, Detroit, Michigan.]

**Effect of carbon tetrachloride poisoning on the toxicity of  $\beta$ -diethylaminoethyl phenyl- $\alpha$ -thienylacetate and benadryl.** JAMES Y P CHEN (by invitation)<sup>1</sup> and BENEDICT E ABREU *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco*. For the preliminary demonstration of the probability that the liver was the organ primarily responsible for the detoxication of  $\beta$ -diethylaminoethyl phenyl- $\alpha$ -thienylacetate (DPT), a new antispasmodic agent, two dogs were selected, one chronically poisoned by CCl<sub>4</sub> as evidenced by definite hepatic dysfunction, and the other, a normal control. The CCl<sub>4</sub> poisoned dog was able to survive only four daily increasing doses of DPT (5, 10, 20 and 40 mg/kg subcutaneously), dying in convulsions from the fifth dose, 80 mg/kg. The control dog died in convulsions when the dose was increased to 446 mg/kg after it had received daily doses of 5, 10, 20, 40, 80, 160, 225 and 317 mg/kg. Results of this experiment indicate that the liver probably plays an important role in the detoxication of DPT in the dog.

When DPT was similarly administered chronically to normal and CCl<sub>4</sub> poisoned rats, no significant difference in toxicity appeared in these two groups of animals. Similar results were obtained with benadryl in the rat. However, when DPT and benadryl were administered in single toxic dosage to normal and CCl<sub>4</sub> poisoned rats, it appeared that hepatotoxic dosage of CCl<sub>4</sub> influences the ability of the rat to detoxify DPT, but not benadryl. A single dose of 160 mg/kg of DPT killed three of the six (50%) CCl<sub>4</sub> treated rats while the same dose caused no death in the six normal control rats. With benadryl, a single dose of 141 mg/kg killed all six (100%) CCl<sub>4</sub> treated rats and also four of the six (66%) controls. [Aided by a grant from Frederick Stearns & Company, Detroit, Michigan.]

**Cyclic changes in human uterine pressure curves and the influence of distention and pitressin upon**

<sup>1</sup> Now at Department of Pharmacology Tulane University Medical School New Orleans, La.

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these curves GEORGE P. CHINN (by invitation), R. A. WOODBURY, RICHARD TORPIN (by invitation), W. S. BOYD (by invitation), J. L. ALLGOOD (by invitation), J. C. NEAL (by invitation), and H. L. CHESNINE (by invitation) *Depts of Pharmacology and Obstetrics and Gynecology, Univ of Georgia School of Medicine, Augusta, Georgia* The contraction patterns of the human uterus were studied by introducing small water filled balloons into the uterus and recording the pressure changes in the balloons with a Hamilton Manometer. The effects of different drugs and hormones were obtained at various times during the menstrual cycle. The uteri were also subjected to slight distention by increasing the balloon volume. The contraction patterns and drug effects were compared with the non distended uterus.

Although the prevailing pattern of high frequency and low amplitude were obtained during the estrogenic phase and low frequency high amplitude were obtained during the secretory phase, all variations between these types were found. In most patients it was possible to change the estrogenic type to the secretory type by distention.

There was a very low correlation between uterine tone and contraction amplitude. This correlation was increased by pitressin as well as by distention.

With very few exceptions both distention and pitressin increased the tone and amplitude of contractions. Pitressin invariably eliminated any relaxed period if present in the control.

Distention also increased the sensitivity of the uterus to pitressin. The addition of 2 cc to a uterus containing 4 cc, made it possible for 0.1 unit pitressin to produce the same effect as 0.3 units. [These studies were supported by financial grants from Frederick Stearns and Company.]

**Biologic properties of subtilin in physiologic saline solution.** YIN CH'ANG CHIN (introduced by Hamilton H. Anderson) *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco* A portion of subtilin is precipitated in the presence of 0.9% sodium chloride solution. The supernatant fluid which contains 28% subtilin is bacteriostatic against *Lactobacillus plantarum* and *Mycobacterium tuberculosis hominis* in 1:320,000 and 1:800,000 dilutions respectively. It is also amebicidal at 1:400,000. These potencies are comparable to those obtained with aqueous solutions of subtilin. In other words, sodium chloride does not alter the antimicrobial activities of subtilin.

On the other hand, the toxicity of subtilin toward host tissues is reduced by use of physiologic saline rather than aqueous solution. Rabbit leucocytes survive for 60 minutes at 37°C in 1:1000 solution of subtilin in physiologic saline. When subtilin was tested by diluting the initial aqueous

solution with saline, at 1:3,000 concentration half of the leucocytes were immobilized within 30 minutes. The LD<sub>50</sub> of subtilin in physiologic saline solution administered intravenously to mice has been found to be 140 mg/kg in contrast to 100 mg/kg when aqueous solutions were used (Wong, S. and Anderson, H. H., unpublished data). Immediate death followed when 400 mg/kg of the saline solution was given intravenously, in contrast to 200 mg/kg for the aqueous solution. By intracisternal injection in rabbits, 0.6 mg/kg of subtilin in aqueous solution produced convulsions. Fatalities occurred in 50% of animals at this dose. Injection of the same amount of subtilin in physiologic saline solution does not produce convulsions, although a few tremors occur. [Aided, in part, by a grant from Eli Lilly and Company, Indianapolis, Indiana.]

**The effect of Syntropan, Demerol, and Trasentine on gastric secretion.** BYRON B. CLARK *Dept of Physiology and Pharmacology, Albany Medical College, Union Univ, Albany, New York* The effect on gastric secretion of Syntropan, Demerol, Trasentine, and Scopolanine hydrobromide has been compared with the action of atropine sulfate using the Cope pouch dog and the experimental procedures previously described (Am J Physiol, 139:356, 1943). The drugs were administered intramuscularly every three hours corresponding to the three collection periods used. The total effect for nine hours is the basis of the following data.

The per cent depression of volume and acid production with atropine was linear to the log dose between 0.002 and 0.05 mg per kg every three hours, and the threshold dose was 0.001-0.002 mg per kg. Scopolanine had a slightly greater depressant effect on gastric secretion than atropine, while the other drugs were much less active. The threshold dose for Syntropan and Demerol was about 2.5 mg and for Trasentine 3.5 mg per kg. A comparison of the effects of these drugs at the 5 mg per kg level with the dose of atropine producing an equivalent effect indicates that the ratio of activity of atropine to Syntropan and Demerol is 1,000-3,000:1, and to Trasentine over 3,000:1. For example, the depression in acid production by atropine 0.002 and 0.005 mg per kg was 35 and 45 per cent. The amount of depression with Syntropan, Demerol, and Trasentine at 5 mg per kg was 40, 45, and 20 per cent respectively. The depressant effects on volume and acid production were approximately parallel although a slightly greater depression in the acid production was usually observed.

**Some physiologic effects of surface active agents.** V. V. COLE, S. H. HOPPER (by invitation), and H. R. HULPIEU *Depts of Pharmacology and Public Health, Indiana Univ School of Medicine, Indianapolis* Twelve compounds were studied

Seven anionic compounds were used Aerosol OS, Areskline 400, Areskap 100, Aerosol OT, Aresket 300, Santomerse D, and Santomerse 3. Four cationic compounds were used cetyl dimethyl ammonium bromide, Emeol 888, Emulsept, and Tetrosan. One non-ionic compound, Igepal, was studied. Acute toxicities by mouth and vein were determined on mice. There was no constant relationship between toxicities by the two methods. The concentrations producing hemolysis of mammalian red blood cells were determined in vitro. Concentrations producing hemolysis were unrelated to the toxicities by vein. One compound from each group was used for in vivo blood studies on rabbits. The compounds were Santomerse D, cetyl dimethyl ethyl ammonium bromide, and Igepal. None given by vein produced an appreciable effect on cell counts or hemoglobin but examination of smears indicated increased red blood cell destruction. Igepal in non-toxic doses to rabbits and dogs did not influence the distribution of sulfathiazine or sulfathiazole in the blood and spinal fluid. When Igepal was given to guinea pigs infected with tuberculosis it seemed to cause a greater spread of infection. Igepal did not interfere with the repressive action of Promizole on tuberculosis in guinea pigs, and may have increased it.

The curare-like action of ether upon human neuromuscular transmission. J. H. COMROE, JR., R. D. DRIPPS, S. Y. BORLLHO (by invitation) and H. METZ (by invitation). *Depts. of Physiology and Pharmacology, Graduate School of Medicine, and Anesthesiology, Univ. of Pennsylvania School of Medicine*. The effect of ether, pentothal and cyclopropane upon human neuromuscular transmission has been studied by the technique of Harvey and Masland. Supramaximal shocks (3 to 300 per second) were applied to the skin over the ulnar nerve and muscle action potentials were recorded from skin pads over the abductor quinti digiti. In all cases, muscle action potentials obtained in the control period were normal (no decline in amplitude regardless of frequency of stimulation up to 75 per second). Following inhalation of ether anesthesia (5 cases), a change in potential pattern occurred that was quite similar to that observed following intravenous or intra-arterial curare and is believed to be representative of partial neuromyal block. The first potential was often of normal amplitude but the heights of succeeding potentials declined progressively at each frequency for the next 4-5 spikes. This effect was noted at blood ether levels of 100-120 mg % and disappeared promptly upon decreasing the ether concentration. These results upon man tend to confirm the observations of Gross and Cullen (*J. Pharmacology* 78: 358 1913) upon animals (recently denied by Schullik 1916) and indicate that ether has a

curare-like effect upon the neuromyal junction. The decrease in skeletal muscle tone in ether anesthesia is therefore not due wholly to central depression since the peripheral neuromyal junction is depressed at the same time that muscular relaxation appears clinically. Cyclopropane (3 cases) and pentothal (2 cases) anesthesia produced much less effect upon neuromuscular transmission.

Chemotherapeutic activity of cyanines and related compounds in filariasis in the cotton rat. ELIZABETH M. CRANSTON, ASHTON C. CUCKLER (by invitation), JOHN T. LITCHFIELD, JR., THERESA BREY (by invitation), HAROLD N. WRIGHT, and RAYMOND N. BIETER. *Dept. of Pharmacology, Univ. of Minnesota Medical School, Minneapolis, Minnesota*. A group of more than sixty cyanine dyes and related compounds has been studied for chemotherapeutic activity against the natural *Latomosoides carini* infestation in the cotton rat. Compounds were administered chiefly intraperitoneally every eight hours for 18 doses with autopsy on the eighth day. Therapeutic activity was determined by the percentage of dead filaria found 24 hours after autopsy and removal of the worms to a modified Sim's solution. Therapeutic indices were determined as a ratio of M.T.D./M.C.D. employing graded dosages separated from one another by a factor of three.

The majority of the compounds tested were styryl quinolines or diquinolines, and certain rather definite relationships between chemical structure and chemotherapeutic activity were found.

Chemotherapeutic activity was found only in compounds which possessed two nitrogen-containing nuclei, separated by one or more carbon atoms. Considerable activity was found in combinations of quinoline and alkyl substituted aniline and in diquinoline combinations. Activity was considerably enhanced by having one trivalent and one pentavalent nitrogen atom. Activity was also increased by substitution of alkyl or alkoxy radicals in position six of the quinoline ring but was accompanied by increased irritant properties.

This work was done under contract with the Office of Scientific Research and Development, and the Office of the Surgeon General of the U. S. Army, and the University of Minnesota. *Grateful appreciation is accorded to the Eastman Kodak Company and Parke, Davis and Company for supplying these compounds through the Chemotherapy Center.*

The acute and chronic toxicity of nordihydroguaiaretic acid. ELIZABETH M. CRANSTON, MARY JANE JENSEN, ADELAIDE MOREN, THERESA BREY, E. T. BELL and RAYMOND N. BIETER. *Bureau of Plant Industry, USDA, Depts. of Pharmacology and Pathology, Univ. of Minnesota, Minneapolis*.



The acute toxicity of nordihydroguimetic acid (NDGA) was found to be less than that of phenol and catechol on oral administration to mice, rats and guinea pigs and intraperitoneally in mice. Orally in guinea pigs and intraperitoneally in mice NDGA was more toxic than gum guaiac. Orally in mice and rats both NDGA and gum guaiac were relatively non-toxic.

Chronic toxicity experiments over a period of two years were conducted with the drug diet method comparing NDGA with phenol, catechol and gum guaiac in concentrations of 0.25 and 0.5 per cent in mice and 0.5 per cent in rats. Concentrations of 0.1, 0.5 and 1.0 per cent NDGA were used in another series of rats.

NDGA had little or no effect on growth or food intake except in the highest concentration in rats where there was a temporary decrease in growth associated with a decreased food intake. Histological study of the liver, spleen and kidneys showed no significant pathology. Necrosis of the liver was noted occasionally in all groups, including controls. In one series of NDGA rats hemorrhage into the cecum was observed in fifty per cent of the animals. In a larger series of rats on the same concentration of NDGA no such phenomenon developed. Cysts in the mesentery were found in several rats on the higher concentrations of NDGA. Such cysts may occur spontaneously in rats.

Effect of x-ray in vitro upon the contractility of the isolated intestine of the cat. BRADFORD N. CRAVER. Few studies have been made of the effects of x-ray exposure in vitro upon the physiological activity of isolated, contractile, mammalian tissue. With the exception of the study by C. M. Scott (1937), which involved the relatively resistant cardiac tissue, none of them has taken account of a possible latent period that might exist between the time of exposure and the onset of a recordable effect. Accordingly, segments of the small intestine of the cat were exposed at various intervals after their removal from the animal to doses varying from 1000 r to 10,000 r of soft x-rays. The technical factors of the exposure were

120 KV

S Ma

7.5" T S F

640 r/min output

H V L = 1.971 mm aluminum

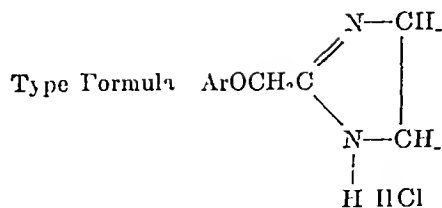
No filter was used save that inherent in the instrument. The spontaneous contractility of control and exposed strips was kymographically recorded at suitable intervals for as long as four days after the animal's death. The length of the latent period between the immersion of the strip in the oxygenated Locke's solution at 39°C and the onset of the spontaneous motility was positively correlated

with the length of time between the death of the animal and the arrangement of the recording. No significant differences between the behavior of the control and the exposed strips were discernible either in respect to the latent period just mentioned or the nature of their recorded contractions. [This abstract is based on work performed under Contract Number W-7401 eng 49 with the Manhattan Project for the University of Rochester, Rochester, New York. Present address: Ciba Pharmaceutical Products, Inc., 556 Morris Avenue, Summit, New Jersey. The author thanks Mr. Robert Hay and Mr. Herbert Mermagen for arranging the roentgenologic exposures and Miss Mildred Taylor for technical assistance.]

The role of adrenal cortical injury in the toxic effects of x-ray exposure. BRADFORD N. CRAVER. Two series of 25 male Wistar rats each were treated as follows: (1) In the "protected" series a lead strip one inch wide was placed over the adrenal region before x-ray exposure, (2) in the "control" series two lead strips one half inch wide were placed above and below the adrenal area to give, insofar as possible, equivalent protection to like tissue. Both series were exposed first to 660 r whole body radiation (excepting areas covered by the strips) and 29 days later were exposed to 880 r. The "protected" series revealed a statistically significant lower mortality and morbidity up to the time of their disposal which was 30 days after the second exposure ( $\chi^2 = 5.3725$ ,  $P = 0.0205$ ). The applications of this finding for the therapy of x-ray induced damage and irradiation sickness will be discussed in the light of the hypothesis, x-ray damages cells, the latter require lymphoid proteins for repair, and these proteins are made available by adrenal cortical activity. [This work was performed while the author was a research associate of the University of Rochester's Division of the Manhattan Engineering Project. Present address: Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey. The author thanks Mr. David Tiedeman for the statistical data, Mr. Francis Bishop for arranging the exposures in this experiment, and Miss Mildred Taylor and Mrs. Florence Van Slyke for technical assistance.]

Some pharmacological properties of imidazoline and aryloxyacetamidine hydrochlorides. BRADFORD N. CRAVER, PATRICIA SEIF (by invitation) and JAMES SMITH (by invitation). Dept. of Pharmacology, Research Division, Ciba Pharmaceutical Products, Inc., Summit, New Jersey. Djerassi and Scholz have already published chemical data concerning the preparation of the above compounds. The present communication concerns their pharmacological properties which may be conveniently summarized in the following tables.

## Imidazoline



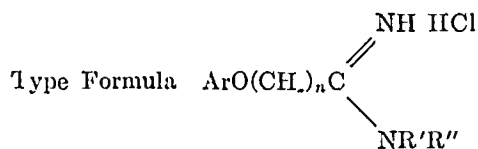
Prep No	ArO	Vs <sup>1</sup> Hist	Vs Ach	Dog blood pressure	
				Dose in mg/kg	Effects <sup>2</sup>
253	2,5-dimethylphenoxy	10-p	0	0.1	++
223	o-toloxoy	0	10-p	0.1	++
213	m-toloxoy	0	0	100	++
218	p-toloxoy	10	0	1	--
180	Thymyloxy	10-p	10-p	0.1	++
189	carvaeryloxy	0	0	0.1	++
252	o-isopropylphenoxy	10-p	10-p	0.1	++
174	phenoxy	10-p	0	1	++
235	3-methyl-4-chlorophenoxy	10-p	10-p	1	0
204	benzhydryloxy	0.1	1	5	-

<sup>1</sup> The numbers in this column represent the doses in  $\gamma/\text{cc}$  that would completely inhibit the spasm induced in an isolated guinea pig ileum by  $1\gamma/\text{cc}$  of histamine added 2 minutes after the test drug. The letter "p" denotes partial inhibition. The test drug was not employed in a concentration exceeding  $10\gamma/\text{cc}$ .

<sup>2</sup> The stimulating dose of acetylcholine was  $0.2\gamma/\text{cc}$ . Otherwise the remarks under "Hist" apply.

<sup>3</sup> Pluses denote hypertension and minuses hypotension. Slight changes are denoted by one sign and more marked changes by two.

## Aryloxyacetamidine Hydrochlorides



Prep no	ArO	R	R''	Vs <sup>1</sup> Hist	Vs <sup>2</sup> Ach	Dog blood pressure	
						Dose in mg/kg	Effects <sup>3</sup>
176	phenoxy	H	H	10-p	0	1	++
207	p-toloxoy	CH <sub>3</sub>	CH <sub>3</sub>	0	0	4.5	++
225	o-toloxoy	H	H	0	0	5	++
224	o-toloxoy	CH	CH <sub>3</sub>	0	10-p	2.2	++
212	m-toloxoy	H	H	10-p	10-p	1	++
211	m-toloxoy	CH <sub>3</sub>	CH <sub>3</sub>	0	0	4	++
217	p-toloxoy	H	H	0	0	7	++
215	p-toloxoy	CH <sub>3</sub>	CH <sub>3</sub>	0	0	2.2	++
179	thymyloxy	H	H	10-p	0	1	++
198	thymyloxy	CH <sub>3</sub>	CH <sub>3</sub>	10-p	0.1	2	0
216	thymyloxy	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	1	0.1	2	--
214	thymyloxy	\ C <sub>6</sub> H <sub>5</sub>	\ C <sub>6</sub> H <sub>5</sub>	10	1	5	--
200	thymyloxy	\ C <sub>6</sub> H <sub>5</sub>	\ C <sub>6</sub> H <sub>5</sub>	1	10-p	1	--

## Aryloxyacetamidine Hydrochlorides—Continued

Prep No	ArO	R'	R''	Vs <sup>1</sup> Hist	Vs <sup>2</sup> Ach	Dog blood pressure	
						Dose in mg/kg	Effects <sup>3</sup>
245	thymyloxy	C <sub>6</sub> H <sub>5</sub> CH CH <sub>3</sub>	H	10	10	5	-
188	carvaeryloxy	H	H	10-p	0	1	0
222	carvaeryloxy	CH	CH <sub>3</sub>	10	1	5	++
208	carvaeryloxy	C <sub>6</sub> H <sub>5</sub> CH CH <sub>3</sub>	H	1	10	1	++
242	3-methyl-4-chlorophenoxy	H	H	1	10-p	4	++
243	3-methyl-4-chlorophenoxy	CH <sub>3</sub>	CH <sub>3</sub>	10	10-p	5	++
250	o-isopropylphenoxy	H	H	10	10-p	5	+-
251	o-isopropylphenoxy	CH <sub>3</sub>	CH <sub>3</sub>	10-p	1	3	--
255	2,5-dimethylphenoxy	H	H	0	0	5	+-
254	2,5-dimethylphenoxy	CH <sub>3</sub>	CH <sub>3</sub>	10-p	10	5	+
185	benzyloxy	H	H	10-p	0	1	++
206	thymyloxy	CH <sub>3</sub>	CH <sub>3</sub>	10	1	5	--
258	$\beta$ -carvaeryloxy	CH <sub>3</sub>	CH <sub>3</sub>	10-p	10	1	--

<sup>1</sup> <sup>2</sup> <sup>3</sup> See notes to previous chart.

Additional data concerning the more interesting compounds will be considered in the presentation.

**Influence of iodine therapy on blood iodine and basal metabolic rate in pregnancy.** NORMAN A. DAVID and F. BERTRAM ZENER (by invitation). *Dept. of Pharmacology, Univ. of Oregon Medical School, Portland, Ore.* The routine administration of iodine to the majority of pregnant women is still based on inadequate knowledge of iodine metabolism during this period. We have attempted to obtain data for correlating the iodine demand in pregnancy with the basal metabolic rate (BMR) and to observe the effect of iodine therapy on these two factors. Normal blood iodine (BI) values (Stevens' method) in 53 non-pregnant normal adults living in the Northwest ranged from  $8.4$  to  $12.4 \gamma/\%$ . Unmarried pregnant girls domiciled for varying periods in a nursing home before and after delivery, and given no supplemental iodine, served as controls. Iodine-treated patients received 1 tablet (0.03 gram) of Lipiodine daily. In the first trimester 12 control patients showed an average BMR of plus 12.1% and an average BI of  $16.2 \gamma/\%$  while in the second trimester in 24 control patients the BMR increased to an average of 22.4% and the BI to  $17.4 \gamma/\%$ . In this trimester the 14 Lipiodine-treated patients had an average BMR of only 10% and an average BI of  $39.7 \gamma/\%$ .

During the third trimester the 61 control patients showed little change in the average BMR which was 23% and in the average BI of 16.05%. However, the 21 iodized patients showed a rise in the BMR to 17.8% and a drop in the BI to 28.4%. Several patients were observed just before delivery. Both groups showed increases in the BMR while in the control group the BI rose slightly and that for the treated group showed a marked rise. At term, the average BI for 35 control patients was 22.6% and for the 24 treated patients, 35.5%. At 6 weeks post partum the 12 controls averaged a BMR of 15.5% and a BI of 12.15%. The average BMR in the 10 treated patients dropped to 11.7% while the BI remained at 12.9%. Correlation of this data shows that a reciprocal relationship exists between the BMR and the BI, a rise or high value in one factor being accompanied by a drop or low level for the other.

Antagonism of the vasopressor action of nicotine by potassium thiocyanate JOHN E. DAVIS and ALFRED H. LAWTON (by invitation) *Dept. of Physiology and Pharmacology, Univ. of Arkansas*. The mechanism by which thiocyanate ion lowers the hypertensive blood pressure is not established. In the effort to elucidate this subject, we have tested in acute experiments on dogs the effects of various pressor drugs and humoral substances upon the blood pressure, both before and after infusing potassium thioevanate intravenously, to build a therapeutic blood concentration. The pressor actions of angiotonin, epinephrine and other peripherally acting substances were apparently not affected by thiocyanate.

In various experiments, either nicotine alkaloid or nicotine sulfate was injected intravenously into dogs anesthetized with pentobarbital sodium (30 mg per kg). Blood pressure recordings were made from a mercury manometer, and anesthetic was given if necessary to maintain a constant plane of anesthesia. After control blood pressure responses to test doses (usually 1 mg) of nicotine had been recorded, potassium thiocyanate solution was injected gradually and allowed to distribute itself for about 45 minutes. After variable lengths of time, and after serum thiocyanate levels varying from 12 to 24 mg per cent had been reached, the blood pressure elevation responses to nicotine were reduced by 35 to 66 per cent. Control animals, not given thiocyanate, showed fairly uniform, undiminished responses to nicotine over periods as long as 5 hours. In some thiocyanate experiments atropine was used, in others it was not. An early effect of thiocyanate appeared to be an increased sensitivity to nicotine pressor action. We suggest that thiocyanate may affect autonomic ganglion cells. The study is still in progress.

The effects of toxic doses of thiouracil on the reproductive system of the male rat M. EDWARD

DAVIS (by invitation) and NICHOLAS W. FUGO *From the Dept. of Obstetrics and Gynecology and the Dept. of Pharmacology, The Univ. of Chicago and The Chicago Lying-in Hospital*. Twenty-eight adult male rats weighing from 250 to 425 grams at the initiation of the experiment were treated with thiouracil (0.25% solution as a sole source of drinking water) for a period of 75 to 145 days in the various experiments. Twenty-five other animals of the same weight range served as controls.

At the end of the experimental period the animals were sacrificed, the genital organs, thyroid, adrenals and pituitaries were weighed and examined histologically. The acetone dried anterior pituitaries of treated and control animals were assayed for gonadotropic potency in 21-day immature female rats.

It was found that the reproductive organs of the treated animals showed in all cases various stages of atrophy. The seminal vesicles, testes, epididymes weighed approximately 50% of these organs in control animals of the same weight at the termination of the experiment. The thyroids increased in weight 2 to 5 times over control glands. The adrenals and pituitaries were slightly heavier in experimental animals.

Histologically the genital organs of the treated rats showed marked degenerative changes. In the testes many tubules were aspermatogenic. The seminal vesicles and epididymes showed changes similar to those encountered in castration.

Assays of treated and control anterior pituitaries in 21-day female rats showed no significant differences in the gonadotropic content of these glands.

The effect of alloxan diabetes on reproduction in the female rat M. EDWARD DAVIS (by invitation), NICHOLAS W. FUGO, and KENNETH G. LAWRENCE (by invitation) *From the Dept. of Obstetrics and Gynecology and the Dept. of Pharmacology, The Univ. of Chicago and The Chicago Lying-in Hospital*. The relationship between alloxan diabetes and reproduction was studied in the rat. Estrus cycles of adult female animals were followed carefully and blood sugar determinations were made on alternate days using Somogyi's micro modification of the Schaffer and Hartmann method.

When the fasting blood sugar levels were found to be constant the female animals during estrus were placed with males of known fertility. When sperms were observed in the vaginal smears the animals were injected intravenously with 40 mg of alloxan per kilogram of body weight.

Thirty-seven of the 38 treated animals developed diabetes. In four the hyperglycemia was transient in character lasting one to four days following which the blood sugar levels returned to normal. Thirty-three animals developed perma-

nent diabetes and their fasting blood sugar levels ranged from 150 to 500 mg per cent. The diabetic state persisted until the animals succumbed or were sacrificed. The diabetic animals became pregnant as evidenced by the placental sign on the twelfth day of gestation and by autopsy. Only 5 of the 33 rats survived the entire gestation period of 21 days. Two of these delivered macerated placentas with no gross evidence of fetuses. One animal sacrificed on day 21 of the pregnancy revealed 6 implantation sites with attached placentas but no visible fetal tissue. The remaining 2 animals revealed recent placental sites after the 21 day gestation period.

Control rats and those with transient diabetes delivered normal litters.

The factors responsible for the abnormal pregnancies encountered in alloxan diabetes are under investigation at the present time.

**Experimental chemotherapy of schistosomiasis**  
**2. Comparison of effects of specific drugs**  
 ARTHUR C. DEGRAFT and MAXWELL SCHUBERT (by invitation). At present, the antimonials are the only compounds which furnish drugs of practical value in the treatment of schistosomiasis. The first gross effect of antimony compounds observable on *S. mansoni* in white mice is that the distribution of the worms in the mouse is changed. Generally after a few days treatment the worms all collect in the liver and become unpaired though the average number of worms per mouse is not changed. Egg passage in the feces ceases. If treatment is stopped at this point, the parasites may reascend the mesenteric veins, pair again and resume laying eggs. Egg passage in the feces begins again and a complete picture of relapse is produced.

Using methods previously described, an attempt has been made to compare as quantitatively as possible the effectiveness of a variety of trivalent and pentavalent antimonials. Under the conditions of test, wide variations are found in effectiveness of antimonials. Some of the pentavalent compounds such as neostibosan, which in the past have been little used clinically, are as effective as commonly used trivalent compounds such as fuaadin. A few new antimonials are recorded with a higher therapeutic efficiency than any that have previously been used clinically. One new antimonial was found to be highly effective when fed.

In a search for new types of compounds that might have value as drugs, over three hundred organic compounds of varied structure were screened but none showed any definite value. A few that showed slight promise are discussed.

**The immediate toxicity of hexaethyltetraphosphate, tetraethylpyrophosphate, and hexaoctyltetraphosphate to rabbits and rats**  
 WM. B. DEICHMANN and S. WITHERUP (by invitation). *From the Kettering Laboratory of Applied Physiology, College*

*of Medicine, Univ. of Cincinnati, Cincinnati, Ohio*. Hexaethyltetraphosphate and tetraethylpyrophosphate have been suggested as biological agents. Since the manufacture and handling of these compounds may involve certain risks, experimental observations were made to determine certain preliminary facts as to their toxic effects.

When absorbed from the alimentary tract or through the skin in sufficient quantity, hexaethyltetraphosphate and tetraethylpyrophosphate induced an acute toxic state characterized by an increase in respiratory movements, hyperexcitability, tremors (persisting after death), convulsions, dyspnea, collapse and death as a result of respiratory failure.

When given orally to rats the approximate single lethal dose of hexaethyltetraphosphate (0.1 per cent aqueous solution) is 0.005 ml/kg, the corresponding lethal dose of tetraethylpyrophosphate is 0.002 ml/kg.

A decrease in the degree of toxicity occurs when aqueous solutions are permitted to stand. Thus, hexaethyltetraphosphate when left at room temperature for 24 hours as a 1.0 per cent aqueous solution, decreased in toxicity from 0.005 to 0.18 ml/kg, tetraethylpyrophosphate decreased in toxicity from 0.002 to 0.16 ml/kg (determined similarly), and after a period of three days to 0.28 ml/kg.

The lethal dose of hexaethyltetraphosphate (2.5 per cent aqueous solution), when applied upon the abdominal skin of rabbits, appears to be roughly 0.08 ml/kg. Half of this dose of the pyrophosphate killed a rabbit in 35 minutes. Obviously these substances are readily absorbed through the skin.

The immediate toxicity of hexaethyltetraphosphate is low. When given orally to rats the single lethal dose of the undiluted material is 10.0 ml/kg. The signs of poisoning observed included mild hyperexcitability, generalized weakness, dyspnea and collapse.

**Influence of endocrine imbalance on middle ear structure**  
**I. Histological study in white rat**  
 HAROLD DE MARS, GUY BOYDEN, BEN VIGGOFF, and E. HENDRICKS (introduced by N. David). *Dept. of Pharmacology, Univ. of Oregon Medical School*. Clinical evidence has suggested that hearing may be affected by endocrinopathies such as hypothyroidism and hypogonadism while some experimental work on otosclerosis indicates that structural and developmental changes in the middle ear are associated with pathological changes in the endocrine glands. We have started a complete anatomical and histological study of the middle ear of the normal rat for each month of age up to six months and at four-month periods from 6 months to 2 years. In addition, the body weight ratio for the various endocrine glands and the histological description is being made for each

period of age. A method has been devised for histological examination of the middle and inner ear which allows sectioning to show the ossicles in proper relationship with the base of the stapes in the fenestra ovalis and including the membranous portions. We are now engaged in investigating the effects of the administration of various hormonal substances on the middle ear, endocrine glands, oxygen consumption, and body weight in comparison with the normals we have established.

**Catalasuria as a sensitive test for uranium poisoning.** ALEXANDER DOUNCE (introduced by Raymond N. Bieler) *Division of Pharmacology and Toxicology, Dept. of Radiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* Furth and collaborators<sup>1</sup> showed that alkaline phosphatase appeared in the urine of animals poisoned by injections of uranium. This suggested the investigation of phosphatasuria and later of catalasuria as possible sensitive tests for uranium poisoning.

After the injection of soluble uranyl salts in dogs, cats, rabbits, and rats, amounts of catalase appear in the urine which depend upon the dose and the species. Catalasuria can be produced by 0.02 gram of uranyl acetate per kg. in rabbits and dogs. Catalasuria goes through a maximum and subsides in approximately one week. The time of onset depends upon the dose.

Soluble tetravalent uranium compounds also caused catalasuria but to a lesser extent. Other agents which damage kidney tubules such as mercury, mapharsen, and tartrate, produced catalasuria.

The source of the urinary catalase appearing after the injection of soluble uranium salts was shown to be the tubular cells of the kidney which are damaged by the uranium. The catalase test is specific for tubular damage in the absence of easily observable numbers of erythrocytes in the urine (less than 400,000 per ml.), or considerable numbers of white cells or bacteria.

The urinary catalase test is best used together with the urinary protein test. With the exception of a single animal the catalase test was found to be somewhat more sensitive than the protein test.

Inhalation of soluble uranium compounds by rabbits and dogs also has caused catalasuria. Catalasuria and proteinuria occurring after such exposure is generally transient.

**Studies on diffusion respiration. III. Changes in alveolar gases and pH of venous blood.**<sup>2</sup> WILLIAM B. DRAPER, RICHARD W. WHITEHEAD and JOSEPH N. SPENCER (by invitation) *From the*

*Dept. of Physiology and Pharmacology, Univ. of Colorado School of Medicine* Roth, Whitehead and Draper (1945) demonstrated that dogs could survive forty-five minutes of diffusion respiration. In the present study, the animal's head was placed in an oxygen chamber. After forty-five minutes of breathing pure oxygen in order to partially denitrogenate the animal, respiratory movements were abolished and prevented from returning by pentothal. After thirty minutes, the alveolar carbon dioxide tension became sufficiently depressant to maintain respiratory arrest without the addition of further anesthetic. Venous blood samples and alveolar gas samples were taken as controls and at regular intervals during the experiment. At the end of forty-five minutes of respiratory arrest, the animal was resuscitated by running a stream of oxygen down the trachea. The results obtained on twelve dogs may be summarized as follows:

Alveolar CO<sub>2</sub> and O<sub>2</sub> Percentages and pH (Venous Blood)

	Averages		
	O <sub>2</sub>	CO <sub>2</sub>	pH
Control under anesthesia	85.9	6.2	7.4
After 15 min. diff. resp.			7.05
After 30 min. diff. resp.			6.89
After 45 min. diff. resp.	28.3	54.7	6.78
15 min. after resump. spont. resp.			7.10
30 min. after resump. spont. resp.		6.3	7.25
60 min. after resump. spont. resp.		4.8	7.32

Eleven of the twelve animals used survived until sacrificed at the end of the fourth week, one died 96 hours after the experiment from unknown causes.

**Failure of benadryl and pyribenzamine in experimental skin sensitization to penicillin and horse serum.** ROBERT H. DREISBACH *Dept. of Pharmacology and Therapeutics, Stanford Univ. School of Medicine, San Francisco 15, California*

Using the experimental allergic skin reaction to penicillin (Arthus phenomenon) in rabbits demonstrated by Chu and Cutting (*Proc. Soc. Exp. Biol. Med.*, 1946, 63: 347), benadryl and pyribenzamine were tested for their protective actions.

Commercial calcium penicillin, commercial sodium penicillin and horse serum control were used as antigens, injected subcutaneously at 6 to 14 day intervals. Commercial streptomycin produced no reactions. Citrinin, and calcium penicillin in beeswax and peanut oil, proved too irritating.

Benadryl injected subcutaneously (5 mg./kg.) twice daily and increased to 3 times on the day of injection of antigen, had no effect on the typical skin reactions from calcium penicillin (5000 units in 1 cc. saline solution) or 1 cc. of a 1 to 10 dilution of horse serum in saline. The same dosage of pyri-

<sup>1</sup> Breeds, C. Flory, C. M. and Furth, J., *Arch. Path.* 36: 402 (1942).

<sup>2</sup> Supported by grants from the Office of Naval Research, the Ella Sachs Plotz Foundation, and the Abbott Laboratories.

benzamine subcutaneously was ineffective in preventing reactions from calcium penicillin 5000 units, sodium penicillin 8000 units, or of dilutions of horse serum, each in 1 cc saline

Mixtures of 1 mg of benadryl or pyribenzamine with calcium penicillin produced reactions similar to control injections of penicillin alone, in penicillin sensitized animals. One mg doses of the same drugs were also ineffective in inhibiting reactions when mixed with dilutions of horse serum in sensitized animals. However, mixtures of benadryl or pyribenzamine, with histamine did not produce wheals.

Thus an experimental basis for the claimed beneficial actions of benadryl and pyribenzamine in clinical skin reactions to penicillin is not demonstrable.

Some autonomic nervous system responses to benadryl. N B DREYER and CLEVELAND DENTON (by invitation) *Dept of Pharmacology, Univ of Vermont*. Benadryl has pronounced anti-histamine action on the bronchial musculature. Since histamine is a musculo-tropic agent it is probable that Benadryl acts at the same site. This, however, is not its only site of action, since dryness of the mouth occurs in Benadryl therapy.

Experiments were carried out to test the effect of Benadryl on the autonomic nervous system. The duct of the submaxillary gland of a decerebrated cat was cannulated. The chorda tympani and cervical sympathetic were isolated and sectioned, and the peripheral ends were stimulated for 20 seconds with tetanizing current of submaximal intensity. Stimulation of the sympathetic followed 40 seconds after the cessation of stimulation of the chorda tympani. Stimulation under these conditions of the sympathetic caused a good salivary flow. The left vagus was sectioned in the neck, and the peripheral end was stimulated for 30 seconds for its effects on the motility of the stomach and small intestine.

Benadryl, 15 mg per kg intravenously caused a diminution in salivary flow on chorda tympani stimulation, it had no effect on the sympathetic. Five mg per kg intravenously, paralyzed chorda tympanic secretions completely. Four hours after the injection the chorda began to recover, at the end of five hours chorda tympanic effects had returned to normal. Stimulation of the sympathetic nerve also gave a lessened secretion, but this was never completely abolished. On the intestine, Benadryl, 2.5 to 5 mg per kg lowered the tonus and diminished motility. Motor responses to vagus stimulation were also diminished. The rate of recovery of the intestine paralleled that of the chorda tympani on the salivary gland. Repeated injections of Benadryl led to tachyphylaxis and eventually to a reversal effect, giving a motor response.

A method for testing anti-spasmodics on the cat's intestine in situ. N B DREYER and DONALD HARWOOD (by invitation) *Dept of Pharmacology, Univ of Vermont*. Isolated pieces of intestine suspended in oxygenated Ringer's fluid after Magnus' method can be thrown into spasm by various drugs. Barium chloride and acetylcholine are frequently used for this purpose. In the cat or dog, increased tonus of the intestine can be produced by administering morphine parenterally. In all these cases a drug is used to produce hypertonus. Increased tonus of the intestine is more likely of neurogenic origin. In order to obtain neurogenic hypertonus in cats the following procedure was adopted.

Cats were decerebrated under ether anesthesia, the major splanchnic nerves were isolated, a strong thread was looped around each, the adrenals were removed. Movements of the upper small intestine were recorded from two segments prepared after method of Roger, but modified to the extent of using corn oil instead of isotonic salt solution as the filling fluid. The cat was immersed in a bath of Ringer fluid kept at 36°C. When movements became stabilized the splanchnics were severed by ripping with the loops of thread. There was an immediate increase in tonus which persisted throughout the experiment, which lasted up to 8 or 10 hours.

As standard anti-spasmodics, papaverine hydrochloride, 2 mg per kg or nitroglycerin, 1 mg per kg were injected intravenously. Nitroglycerin action is short, but that of papaverine is much longer. When the drug action has worn off the tonus returns to its previous level. Other drugs with anti-spasmodic properties can be compared for duration and intensity of action against nitroglycerin and papaverine.

$\beta$ -Ionone, a sympatholytic agent. N B DREYER and DONALD HARWOOD (by invitation) *Dept of Pharmacology, Univ of Vermont*. In a recent report in *SCIENCE* it was mentioned that Ionone was a sympatholytic agent. It was decided to determine whether Alpha and Beta Ionone both acted in this manner.

To test this hypothesis the method of Broom and Clark using isolated strips of rabbit uterus for determining the sympatholytic action of ergotamine was followed, using a 100 cc bath. Epinephrine in concentrations of 1 to 3 million produced a submaximal contraction of the isolated uterus. Propylene glycol, the solvent for  $\beta$ -Ionone, did not interfere with the response of epinephrine.  $\beta$ -Ionone, 50 mg, caused no change in motility or tonus, but diminished the response of the standard dose of epinephrine by 10 to 15%, 1 mg diminished the response by more than 50%, and 1.5 mg abolished the epinephrine response completely. On repeated washing of the strip with Ringer's

fluid, the response to epinephrine could be virtually restored in the course of one hour

Other sympatholytic actions of B Ionone were tested. In the salivary gland of the cat it diminished or even abolished the response to electrical stimulation of the cervical sympathetic nerve, it had no effect on the chorda tympani stimulation. On the blood pressure of the cat, B Ionone, 2 to 16 mg per kg reduced but never abolished the pressor response to epinephrine, 10 mg per kg. In this respect B-Ionone resembles thiourea. B Ionone had no sympatholytic effect on the intestine where the sympathetic is inhibitory. Alpha-Ionone showed only slight sympatholytic action.

Estrogenic changes in normal rats fed a low protein diet. VICTOR A. DRILL and CARROLL A. PHELPS. From the Depts. of Pharmacology and Anatomy of Yale Univ. School of Medicine, New Haven, Connecticut. Castrated female rats with pellets of estrogen in the spleen eventually fail to inactivate the estrogen when liver damage is produced by feeding a low protein diet. Such animals eventually lose weight. If normal animals are used ovarian function will cease at a given level of weight loss. However, in rats with splenic implants of estrogen, estrogen is still being supplied from the pellet. This study was designed to ascertain if in normal animals fed a low protein diet ovarian function would cease first or, if ovarian function remained normal and in the presence of developing liver damage the liver failed to inactivate the estrogen produced by the ovary. Estrogenic changes were followed by vaginal smears. All rats received an adequate yeast intake as a source of the vitamin B complex.

Thirteen rats fed a low protein diet (8% casein—35% fat) showed a cessation of estrous cycles between the 67th and 129th days of the study (Average, 88). At the time of the last cycle the average weight loss was 21.2 grams. Five paired castration control rats fed a normal protein intake (18% casein—35% fat), but each limited to the food intake of one of the low protein rats, showed a cessation of estrous cycles between the 88th and 124th day (Average, 104). Average weight loss at the time of the last cycle was 26.8 grams. Control rats lead normal cycles throughout the study. No evidence of an increased estrogenic effect was obtained in the vaginal smears [funded by a grant from Eli Lilly & Company].

Further studies of anticonvulsant actions of compounds chemically related to isopropyl alcohol. ROBERT L. DRIVER (introduced by P. J. Hanzlik). Dept. of Pharmacology and Therapeutics, Stanford Univ. School of Medicine, San Francisco, Calif. The anticonvulsant and convulsant actions of a large number of compounds related in chemical structure to isopropyl alcohol were studied in rats using the electroshock method

(Driver Proc. Soc. Exp. Biol. Med., in press). The thresholds for clonic convulsions were determined 1 hour after the gastric administration of the agents. A total of 150 rats was used, generally 5 for each drug. Dosage of 25 of the 28 compounds tested was 1250 mg/kg, same as previously for isopropanol.

The following compounds produced significant increases in thresholds in non-depressant dosage unless otherwise indicated: isopropyl-urea (slight depression), methyl isopropyl ketone, isophorone (toxic), diacetone alcohol monomethyl ether, glycerol- $\alpha,\gamma$ -disopropyl ether (marked depression), methylethyl ketone.

The following were ineffective but some were toxic: acetyl acetone, isovaleryl acetone, mesityl oxide, 2-acetoxy-4-methoxymethyl pentane,  $\beta,\beta',\gamma,\gamma'$ -tetrachlorodipropyl ether, glycerol-1-monoisopropyl ether, disobutyl ketone, 3,3,5-trimethylecyclohexanol, methylisobutyl carbinol,  $\alpha,\beta$ -dichloroisobutyric acid, 2-ethyl-4,4,6-trimethyl-1,3-dioxane, isopropyl sulfolanylamine, N-isopropylacetanimine, N-isopropylisobutylaldehyde.

The following significantly lowered the thresholds: isopropylamine, diacetondiamine, N-isopropylbutylamine, N-isopropyl-n-propylamine. Doses of these agents were 500 mg/kg, except diacetondiamine (1250 mg).

Of considerable interest was the fact that, in some compounds, the simple substitution of an amino group for a hydroxyl group converted an anticonvulsant into a convulsant and reversed the raised threshold, for example, isopropyl alcohol (anticonvulsant) increased the threshold 82%, while the same dose of isopropyl amine (convulsant) decreased it 20%. In general, complex ketones and related compounds offer no advantage for anticonvulsant action over the simplest ketogen, isopropanol, whose action can be reversed by an amine.

Comparative anticonvulsant actions of isopropyl alcohol, diphenylhydantoin, phenobarbital and tridione. ROBERT L. DRIVER and G. L. ORDWAY (introduced by P. J. Hanzlik). Dept. of Pharmacology and Therapeutics, Stanford Univ. School of Medicine, San Francisco, Calif. A comparative study was made in rats, rabbits and cats (79 animals) of 3 well known antiepilepsy drugs and isopropyl alcohol recently found to have marked anticonvulsant actions (Driver Proc. Soc. Exp. Biol. Med., 1947, in press). Clonic convulsions were produced by the electroshock method (Chu and Driver Proc. Soc. Exp. Biol. Med., 1947, in press) 1 hour after gastric administration of each drug or combination. Doses in mg/kg of body weight were: isopropyl alcohol, 1,250,

\* Supplied by the Shell Development Co. Emeryville, Calif.



diphenylhydantoin, 100, phenobarbital, 50, and tridione, 100 Isopropyl alcohol in combination with each of the other 3 drugs resulted in no motor depression or ataxia in any of the animals except those receiving phenobarbital, which was marked, and in the rats receiving isopropyl alcohol plus tridione, which was only slight

Isopropyl alcohol was quite effective in raising the cortical threshold in all 3 species being comparable to diphenylhydantoin, diphenylhydantoin alone was effective chiefly in cats, and tridione was without effect in all 3 species, as might be expected Phenobarbital was effective in all species but always caused motor depression, sometimes bordering on anesthesia

The most marked anticonvulsant activity was obtained with isopropyl alcohol combined with one of the other drugs, except tridione and here it was no greater than that of isopropyl alcohol alone The vast majority of all animals survived

A comparison of cholinesterase inhibitors *in vitro* and *in vivo* KENNETH P DuBois, WILMA F ERWAY (by invitation), and RICHARD U BYERRUM (by invitation) *Univ of Chicago Toxicity Lab and the Dept of Pharmacology, Univ of Chicago* The differences in pharmacological response produced by cholinergic drugs has been attributed to differences in detoxification, dissociation of the cholinesterase-inhibitor complex, and differences in ability to penetrate cells The present experiments indicate that penetration differences greatly influence the site of action of cholinergic drugs

The inhibitory action of three compounds was tested manometrically on rat brain and submaxillary cholinesterase *in vitro* in a system containing 0.01 M acetyl choline and homogenized tissue in calcium free Ringer bicarbonate medium A final inhibitor concentration of  $1 \times 10^{-7}$  M produced the following inhibition Carbamic acid, N,N-dimethyl-4 dimethylamino 3 isopropyl-phenyl ester methiodide, brain 59, submaxillary 70, physostigmine salicylate, brain 58, submaxillary 59, and prostigmine methyl sulfate, brain 41, submaxillary 47 All three compounds were of similar inhibitory action *in vitro*

For *in vivo* studies the drugs were injected subcutaneously into rats and the tissues were removed for cholinesterase measurements at the time of death After a minimum lethal dose the per cent decrease in cholinesterase activity was Carbamic acid, N,N dimethyl-4 dimethylamino-3-isopropyl-phenyl ester methiodide (0.3 mg/kg), brain 0, submaxillary 35, serum 90, physostigmine salicylate (3 mg/kg), brain 30, submaxillary 58, serum 80, and prostigmine methyl sulfate (2.0 mg/kg), brain 5 submaxillary 60, serum 85 The differences in inhibitory action of the compounds *in vitro*

and *in vivo* indicate that penetration is of importance in the site of action of cholinergic drugs and demonstrates the importance of testing cholinesterase-inhibiting drugs *in vivo* in measuring their site of action

The effect of alpha-naphthylthiourea on peroxidase and catalase KENNETH P DuBois and EMIL E SEBESTA (by invitation) *Univ of Chicago Toxicity Lab and the Dept of Pharmacology, Univ of Chicago* Previous investigations have indicated that thiourea and related compounds inhibit the oxidation of certain substrates as catalyzed by peroxidase In connection with the mechanism of acute poisoning by the rodenticide, alpha-naphthylthiourea (ANTU), we wished to ascertain whether this thiourea derivative interfered with peroxidase-catalyzed reactions ANTU was found to inhibit the oxidation of benzidine, p-aminobenzoic acid, and epinephrine as catalyzed by rat lung peroxidase The lack of sufficient information regarding the presence of peroxidase in animal tissues necessitated peroxidase assays before significance could be attached to interference with this enzyme in acute ANTU poisoning

A modification of previous peroxidase methods was devised to employ small quantities of tissue and this method was applied to several perfused rat and guinea pig tissues since rats are susceptible and guinea pigs resistant toward the rodenticide These measurements showed that rat and guinea pig tissues exhibit peroxidase activity The descending order of activity for guinea pig tissues was liver, adrenals, kidney, lung, spleen, cardiac muscle, pancreas, skeletal muscle, and brain, and for rat tissues was liver, kidney, spleen, lung, thyroid, cardiac muscle, adrenals, pancreas, skeletal muscle, and brain Most guinea pig tissues exhibited higher activity than rat tissues with the high guinea pig adrenal activity being the most marked species difference

ANTU had no direct effect on catalase activity *in vivo* nor *in vitro* Considerable species variations in catalase activity were noted with the high catalase activity of guinea pig adrenals being the most pronounced difference

The renal clearance of penicillins F, G, K, and X, and of bacitracin in rabbits and man HARRY EAGLE and ELLIOT V NEWMAN (by invitation) *Lab of Experimental Therapeutics of the U S Public Health Service and The Johns Hopkins School of Hygiene, and the Dept of Medicine of The Johns Hopkins Medical School* 1 The renal clearance of penicillins F, G, and X in man was found to approximate the total renal plasma flow, and was approximately 4 to 5 times greater than the glomerular filtration rate as determined with inulin or sodium thiosulfate The

penicillin clearance was independent of the absolute blood level over the entire range 0.05 to 10 micrograms per cc, and was similarly independent of the rate of urine flow

2 The possibility is suggested that penicillin can be used in lieu of PAHA or diodrast as a test of renal plasma flow and renal function

3 The renal clearance of penicillin K in man varied from  $\frac{1}{4}$  to  $\frac{1}{2}$  that of F, G, or X

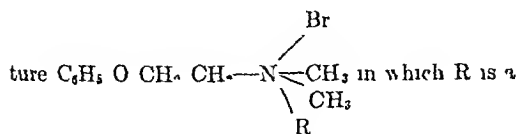
4 The tubular excretory mechanism was completely saturated in 2 rabbits receiving 600 mg/kg of penicillin G. In these the initial blood levels were 2667 and 3200 micrograms per cc, and the initial renal clearances of 3 and 7 cc per minute corresponded to the glomerular filtration rate. As the serum concentration fell to less than the saturation level for the tubular mechanism, the renal clearances rose to normal levels of 22 and 45 cc per minute

5 Antibiotic concentrates derived from culture filtrates of *B. subtilis* (Tracy) have been studied with respect to blood levels, urinary excretion, and renal clearance

a) In eight rabbits injected intramuscularly or intravenously with 0.6 or 6.0 mg/kg, the renal clearance of bacitracin varied from 2 to 7 cc per minute, averaging 4.1. This is less than the average glomerular filtration rate in rabbits. In contrast, the renal clearances for penicillins F, G, and X of 18 to 100 cc per minute, averaging 40 to 45 cc, approximate the total renal plasma flow in that species

b) The renal clearance of bacitracin in 9 human subjects varied from 105 to 233 cc per minute, averaging 159 cc. The renal clearance of bacitracin averaged 1.1 times the glomerular filtration rate as determined with sodium thiosulfate, and was  $\frac{1}{10}$ th of the calculated renal plasma flow in those subjects

**Bacteriostatic and bactericidal properties of  $\beta$ -phenoxy ethyl-dimethyl-dodecyl-ammonium bromide (PDDB) and as a skin and instrument disinfectant** P. C. EISMAN, M. ROXBART, F. C. KULL and R. L. MAYER (introduced by Frederick F. Yonkman) A series of compounds of the struc-



normal alkyl chain of 10, 12, 14, 16, etc. carbon atoms or combinations of them, were found to exhibit significant bacteriostatic and bactericidal properties. The most active of these compounds was the dodecyl derivative (W. Bosshard & L. Neipp, in press). As with other quaternary am-

monium salts, it is particularly effective in regard to gram-positive organisms. Under our experimental conditions it exhibited, for instance, bacteriostatic activity against *Staph. aureus* in a concentration of 1:200,000, *Shigella paradysenteriae* 1:96,000, *Mycobacterium tuberculosis* No. 607 1:50,000, *Trichophyton interdigitale* 1:192,000. The phenol coefficient for *E. typhosa* is 275, and that for *Staph. aureus* 469 at 37°C. Organic matter, such as blood serum or citrated blood, diminishes the activity against gram-negative organisms to a greater degree than against *Staph. aureus*. Soap similarly interferes markedly with the antibacterial activity of this compound, a characteristic which is common to cationic detergents. At pH 8.0 the activity is eight times greater than at pH 5.3.

The activity of PDDB upon contaminated surgical instruments was tested by Spaulding's method (Surg., Gynec. and Obstet. 69:738, 1939). Scalpel blades contaminated with suspensions of various organisms in blood or pus were treated with a 1:1000 aqueous solution of the disinfectant. One group of contaminated blades was dried at 37°C before testing, using various organisms (*Staph. aureus*, *Pseudomonas*, *E. coli*, *Anthrax* and *Tetanus bacilli*); the blades were sterilized within a contact period varying from less than  $\frac{1}{2}$  minute to 2 minutes in the case of gram-positive organisms and  $\frac{1}{2}$  to 10 minutes with gram-negative rods. The end points were slightly higher when dried blades were used.

The effectiveness of PDDB on the disinfection of human skin surfaces was tested according to the technique described by Gardner (Lancet, May 11, 1946, page 683). Skin contaminated with *Staph. albus* or *Aerobacter aerogenes* and treated with aqueous solution of disinfectant 1:1000 showed approximately 90% reduction of organisms after 1 minute of contact, while virtual sterilization was effected in 2 minutes.

**Comparative effects of 1:1-diphenyl-1-(dimethylaminoisopropyl)-butanone-2 (10820), demerol, and morphine on the respiration of rat cerebral cortex slices** HENRY W. ELLIOTT (introduced by Hamilton H. Anderson) *Division of Pharmacology and Experimental Therapeutics, Univ. of California Medical School, San Francisco* The effects of various concentrations of 10820, demerol and morphine on the  $Q_{O_2}$  of rat cerebral cortex slices in modified Krebs glucose-ringer-phosphate solution have been determined by means of the Warburg technique. The rate of oxygen uptake was followed for ninety minutes before, and ninety minutes after addition of the drug, each slice thus serving as its own control. The findings are summarized in the following table:

Concentration	10820
	Effect on $Q_{O_2}$
0.005M 0.002M	60% inhibition within 30 minutes 97% inhibition at 90 minutes
0.001M 0.00062M 0.0005M	Initial stimulation of approximately 10% followed by partial inhibition at 90 minutes
0.00031M 0.00025M	12% stimulation at 45 minutes falling off towards control rate at 90 minutes
0.00016M	11% stimulation at 90 minutes
0.00008M	No effect
Demerol	
0.01M 0.0075M	95% inhibition at 90 minutes
0.005M	45% inhibition at 90 minutes
0.0025M 0.0012M	No significant inhibition
Morphine	
0.01M 0.005M	No significant inhibition

In agreement with the findings of other works (Seevers, M. H. and Schideman, F. E., *J. Pharmacol.* 71: 373, 1941), morphine has been found to have little effect on brain slice respiration even in the relatively high concentrations studied. 10820 is approximately ten times as potent as demerol as an inhibitor of cellular respiration. While 10820 exerts inhibitory effects at concentrations above 0.0005M, concentrations between 0.0005M and 0.001M produced stimulation followed by inhibition. Concentrations below 0.0005M produced stimulation only. Neither morphine nor demerol in any concentration used produced stimulation.

In view of the fact that all three compounds have similar analgesic properties when administered to the intact mammal it is of interest to note that they exert markedly different effects on brain tissue metabolism. These data indicate that further comparative studies may explain differences in mode of action. [Aided by a grant from The National Institute of Health, Bethesda, Md.]

Carbon tetrachloride liver damage and acetylcholine esterase activity in the rabbit and rat. SYDNEY ELLIS<sup>1</sup> (by invitation), SHIRLEY SANDERS (by invitation) and OSCAR BODANSKY<sup>2</sup> *Biochemis-*

*try Section, Medical Division, Chemical Warfare Service, Edgewood Arsenal, Maryland*. Acetylcholine hydrolysis by plasma enzymes is low in patients with liver disease. The present studies were undertaken to determine the relation between the acetylcholine hydrolyzing capacity of liver and plasma enzymes after carbon tetrachloride administration to animals.

We found that, prior to administration of carbon tetrachloride, the day-to-day variation in the acetylcholine hydrolytic activity of the plasma was large in normal rabbits, whereas rats maintained a rather constant plasma activity. In rabbits, 0.05 to 0.5 cc carbon tetrachloride per kg per day i.p., sufficient to decrease the bromsulphalein clearance and to cause severe pathological changes in the liver, failed to modify the plasma or liver acetylcholine hydrolytic activity. In contrast, in the rat, as was found by Brauer and Root (*J. Pharmacol. Expt. Ther.* 88: 109, 1946), carbon tetrachloride damage reduced the acetylcholine hydrolyzing ability of both plasma and liver. These results indicate that the liver may be the regulator of the acetylcholine esterase activity of the plasma.

Determination of the rates of hydrolysis of acetylcholine, benzoylcholine and acetyl-B-methylcholine by plasma and liver gave the following ratios:

	Acetyl B Methylcholine Acetylcholine	Benzoylcholine Acetylcholine
Rabbits	0.6-0.9	0.1-1.8
Rats	0.1-0.3	0.14-0.22

These results indicate that the enzymes hydrolyzing acetylcholine in the rabbit are either different from those in the rat, or are the same enzymes in different proportions.

Alloxan Diabetes in Thymectomized Rats. G. A. EMERSON, P. L. EWING and THURLO B. THOMAS (by invitation). *Dept. of Pharmacology, Univ. of Texas Medical Branch, Galveston, and Dept. of Zoological Sciences, Carleton College, Northfield, Minnesota*. Ribonucleotides have been shown to be prophylactic in alloxan diabetes. A systematic study was undertaken to observe effects of ablation of nucleoprotein-rich tissues on the course of alloxan diabetes subsequently induced. Thymectomy by the method of Segaloff greatly increased susceptibility of rats to diabetogenic effects of 0.18 and 0.25 mM/kg of alloxan given intravenously; neither thymectomized nor intact rats responded to 0.125 mM/kg. Splenectomy or castration had no comparable effect. Antagonism of alloxan diabetes in normal and operated animals by nucleotides, purines and pyrimidines is being studied.

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<sup>2</sup> Formerly Lt Colonel, A. C. A. U. S. Present address: Dept. of Pharmacology, Cornell Medical College, New York City, New York.

**Acute toxicity of benzedrine sulfate** P L EWING and G A EMERSON *Dept of Pharmacology, Univ of Texas Medical Branch, Galveston* Estimation of the acute toxicity of benzedrine sulfate is difficult since several variables may influence it 100-1000% The importance of environmental temperature and aggregation, emphasized by M R Chance et al, has been confirmed Barometric pressure, relative humidity, light, absorptive site and infection are other factors under investigation [This study was supported by a grant from Smith, Kline & French Laboratories, Philadelphia]

**Influence of optical isomers of amphetamine on maze performance in rats** P L EWING and G A EMERSON *Dept of Pharmacology, Univ of Texas Medical Branch, Galveston* A 16 choice multiple-T maze was employed, with a 48 hour thirst as motivation Varying doses of *d*- or *L*-amphetamine were injected subcutaneously  $\frac{1}{2}$  hour before test runs In acute experiments, performance of partially trained treated rats was compared with that of rats with similar training which received saline alone In chronic experiments, rats were injected subcutaneously with one of the isomers or saline before each run, at 2-3 day intervals With doses from 0.5 mg/kg to toxic levels, no evidence of improvement in performance was found with either isomer Complete interference with expected performance occurred after doses of 25 mg/kg of *d* amphetamine or 15 mg/kg of *L* amphetamine [This study was supported by a grant from Smith, Kline & French Laboratories, Philadelphia]

**Influence of rate of administration on therapeutic, irregularity, and lethal dose of some cardiac glycosides** A FARAH and G MARESH (introduced by Otto Krayer) *Dept of Pharmacology, Harvard Medical School, Boston, Massachusetts* Studies were made on over 50 heart-lung preparations of the dog The cardiac glycosides digitoxin, ouabain, digoxin, folinerin, and lanatoside-B were studied A decrease in the rate of administration of all these glycosides led to a lowering of the therapeutic, irregularity and lethal dose With slow rates of administration, these doses reached a minimum value Any further reduction in the rate of administration did not appreciably change these values The highest rate of administration at which these minimal doses are determined is characteristic for each glycoside

The ratio of therapeutic dose to lethal dose and of irregularity dose to lethal dose is not significantly influenced by the rate of administration These ratios are about the same for all the glycosides studied The therapeutic dose is approximately 10-15 per cent of the lethal dose and 20-25 per cent of the irregularity dose

Some inhibitory effects of alkaloids on bac-

terial growth and metabolism R M FEATHERSTONE (introduced by E G Gross) and J R PORTER (introduced by W W Hale) *Depts of Pharmacology and Bacteriology, College of Medicine, State Univ of Iowa, Iowa City* The effect of 37 alkaloids and related compounds on the growth of 26 bacterial species was studied Both meat infusion broth and a chemically-defined medium were employed Of the 37 compounds tested, 15 showed no inhibition for any of the species, 13 exhibited inhibitory action on 1 to 6 of the organisms, whereas 9 of the compounds were strongly inhibitory for 18 or more of the bacteria The inhibitory action of this latter group of compounds, which consisted largely of quinoline derivatives, could not be reversed by the addition to the media of several known growth factors or extracts from plant and animal tissues

In metabolism studies, using standard manometric procedures, several of the quinoline derivatives, such as quinine, quinidine, nupercaine, lepidine, and others, were found to interfere at some stage in the oxidation of glucose and carbohydrate intermediates Several factors were studied, including concentration of the quinoline derivatives, pH, number of organisms, substrate utilization, growth of factors as reversing agents, and others

**Observations on the role of nicotine in cigarette smoke irritation** J K FINNEGAN (by invitation), P S LARSON and H B HAAG *Dept of Pharmacology, Medical College of Virginia, Richmond* Although the subjective irritating action of nicotine alkaloid is well known, its local effects have not been measured adequately by objective methods

Using a previously described method (Finnegan, Fordham, Larson and Haag, *J Pharmacol & Exper Therap*, in press) we have measured the edema producing properties of various concentrations of nicotine alkaloid and of the smoke from cigarettes made of low nicotine tobacco to which nicotine malate had been added so as to result in the concentrations tabulated below

Of the solutions studied (0.001 M, 0.01 M and 0.1 M), none produced measurable edema upon instillation into the conjunctival sac of rabbits, although at the higher concentration enough nicotine was absorbed to produce convulsions

Nicotine content of tobacco (%)	Nicotine content of smoke (mg/cigarette)	Mean of % increase in moisture
0.50	0.55	42.23
1.03	1.23	47.92
1.73	1.83	52.09
2.15	2.47	47.96
2.62	3.01	41.72

That neither nicotine nor its products of combustion contribute significantly *per se* to the edema-producing properties of cigarette smoke is demonstrated by the lack of relationship between nicotine content and degree of edema produced by the smoke

In contrast to the above findings, subjectively, nicotine, both in the form of solution and smoke, proved to be definitely irritating in approximate proportion to its concentration

**The chronic toxicity of chloroquine (SN 7618)**  
O GARTH FITZHUGH and ARTHUR A NELSON  
*Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C* A two-year chronic toxicity study with albino rats showed that chloroquine is toxic in concentrations of 100 p p m or more in the diet. The effects ranged from a slight damage in some animals at 100 p p m to a severe damage in all animals at 800 p p m. All rats on 800 and 1000 p p m died within the first year of the experiment. Significant retardation in growth occurred at dosages of 400 p p m or more. Blood studies showed a leukocytosis, predominantly neutrophilic, at dosages of 800 and 1000 p p m. The characteristic histopathological change produced by toxic dosages of chloroquine was a focal necrosis of striated muscle, especially cardiac muscle, with replacement by fibrous tissue. The degree of damage to the muscles was related to the dosage of chloroquine.

**Procaine studies in tissue applying the Bratton-Marshall method for the determination of sulfonamides** R B FORNEY (by invitation), H R HULPIEU, and V V COLE *Dept of Biochemistry and Pharmacology, Indiana Univ School of Medicine, Indianapolis* During a study of the intravenous use of procaine, it was desired to make quantitative estimations of the concentration in blood and other tissues. We were unsuccessful in obtaining satisfactory results with a method proposed by Bandelin and Kemp (*Ind and Eng Chem*, analytical edition 18 470, 1946) which is essentially a modification of the Bratton and Marshall (*J Biol Chem* 128 537, 1939) method for sulfonamides. We then decided to try the original method without modification. With this we obtained satisfactory results and were able to check solutions of procaine in water within 5 per cent, unknowns made up in blood to within 10 per cent, and unknowns made up in tissue to within 15 per cent. This method, applied directly to urine not containing procaine, gives a color as yet unaccounted for. Procaine was separated from its metabolite, probably para-aminobenzoic acid, by alkaline extraction with ether. Para-aminobenzoic acid may be separated by acid extraction with ether.

Experiments to date with dogs indicate that with 1.5 to 2.5 mg procaine per kg per minute

intravenously, a maximum blood concentration of procaine around 4 mg per cent is reached, para-aminobenzoic acid piles up until death occurs with concentration around 30 mg per cent [*Partly financed by the Office of Naval Research*]

**Some factors concerned in the assay of heparin** R H K FOSTER and A J BEGANI (by invitation) *Dept of Pharmacology, St Louis Univ School of Medicine* Two general procedures were followed: (1) a regular assay technique similar to that previously described (*J Lab Clin Med* 27 820, 1942), (2) observation of coagulation process by means of density measurements with a Fisher electrophotometer. In the assay technique the end-point is the formation of a 50% clot in recalcified, heparinized, citrated beef or sheep plasma. The former method was modified by increasing the amount of calcium and shortening the observation time to 1 hour. The increased calcium steepened the clotting curves which were essentially the same for the two plasmas except in the lower portions where the beef plasma curve declined more gradually. Standard errors were usually less than 1 or 2%.

Fresh plasmas and plasmas stored in the frozen state were studied. On standing a few hours fresh and thawed frozen plasmas required less heparin and gave paler clots but assay results on unknowns (Roche, Wilson) were constant when compared to a standard (Toronto). Thawed frozen plasmas had altered clotting characteristics (no retraction, lowered density, required twice the heparin) but showed no apparent changes attributable to several months storage. Beef plasma clots were markedly denser and easier to read than those of sheep plasma (fresh and frozen plasmas).

Increasing heparin (from zero dose up) retarded the rate of clotting but ultimate clots became progressively denser up to a threshold level following which a rapid change to complete and permanent inhibition ensued. Incubation of plasma with heparin before recalcifying decreased the density of the ultimate clot [*Supported by a grant from the U S Public Health Service*].

**The utilization of an old technique for a sensitive antidiuretic assay** NICHOLAS W FUGO and GLORIA T ARAGON (by invitation) *From the Dept of Obstetrics and Gynecology and the Dept of Pharmacology, The Univ of Chicago and The Chicago Lying-in Hospital* In the search for a sensitive means of determining the presence or absence of small quantities of an antidiuretic substance in the urine of patients with obstetrical complications, the authors have utilized the procedure described in "Laboratory Guide in Experimental Pharmacology" by Edmunds and Cushny, (George Wahr, 1939), for diuretics with the following modifications: a. The rabbit is given water (5% of body weight) by stomach tube 3

hours before start of the experiment b Warm physiologic saline is perfused into the jugular vein at a constant rate of 60-70 drops per minute c Twenty to forty cc of 20% glucose is given intravenously to start the diuresis d The urinary output is measured by continuous reading of the drops excreted per minute

A constant minute output of urine begins in from 30-60 minutes after the initiation of the experiment and is maintained for approximately two to three hours The specimens to be assayed are administered intravenously

The advantages of this method are a Several specimens can be assayed on the same animal for comparative purposes b Each assay requires a fraction of the time employed in other methods c It is possible to quantitate the potency of the unknown substances by comparing with known doses of pitressin at the same time in the same animal d Doses of pitressin as small as 0.0001U give a marked antidiuretic effect

The effect of soil on rodenticide vapor concentrations IRVIN FUHR and SEYMOUR D SILVER (introduced by Stephen Krop) *Gassing and Analytical Section, Medical Division, Chemical Corps, Edgewood Arsenal, Md* Toxic vapors are widely used to control burrowing rodents such as the prairie dog and woodchuck A rodenticide cartridge which liberated cyanides when burned was markedly less toxic in prairie dog burrows than in a metal gassing chamber

These results led to a chamber study on the effect of soil on the persistence of representative toxic gases Results thus far show that soil removes hydrogen cyanide, hydrogen sulfide, sulfur dioxide, and phosgene from air very rapidly In contrast, carbon monoxide was very persistent under these conditions

A carbon monoxide generating mixture was developed The carbon monoxide from 50 grams of mixture was found to be extremely effective on rats in an experimental 250 liter underground burrow It persisted in the burrow for more than 24 hours in a quantity which killed rats in 3 hours

In preliminary field tests a cartridge containing 200 grams of this mixture was 95 per cent effective against woodchucks and 91 per cent against prairie dogs

These results underline the importance of determining the effect of solid or other surfaces when evaluating potential rodenticide or fumigant gases

Explanation of Straub's theory of "potential poisons" based on the measurements of electrical potential differences F GARCIA-VALDE-CASAS (by invitation) and R BEUTNER *From the Depts of Pharmacology of the Univ of Barcelona, Spain, and Hahnemann Medical College, Philadelphia, Penna* Straub's theory (Grenels, Ergeb-

nisse der Physiologie 42 53, (1939)) assumes that drugs like acetylcholine produce their specific action owing to a gradient of their concentrations inside and outside of cells A typical "potential poison" acts only while it penetrates The action ceases after equilibrium has been established The electrical theory (R Beutner, e a ) is based on the finding that acetyl choline or a similar drug changes pre existing phase boundary potential differences, and assumes that this change is the cause of its action The variations of potential differences depend on the relation of drug concentration in aqueous and lipoidal phases,—a magnitude obviously closely related to Straub's gradient Comparative measurements were done with our previously described oil cell using various "oils" including lipoids In one set of "oil" cells the system contained, a priori, no acetylcholine—, this represents the conditions as they exist e g in the denervated mitating membrane which is highly responsive to acetylcholine, (large gradient), in these oil cells 0.0005% of acetylcholine produced variations of 30 to 60 millivolts In another set of oil cells acetylcholine was previously added on both sides of the oil (0.02%)—thus representing conditions existing in the innervated mitating membrane which is less responsive to acetylcholine as it contains some of it a priori, in these oil cells 0.0005% acetylcholine addition produced only a variation of 2-3 millivolts The experiments demonstrate that the presence of acetylcholine exerts a similar influence on phase boundary potential differences and on drug actions

On the toxic reactions of unsaturated lactones and their saturated analogs<sup>1</sup> N J GIACOMINO<sup>2</sup> (by invitation) and E L McCawley *From the Dept of Pharmacology and Toxicology, Yale Univ School of Medicine, New Haven, Connecticut* Evidence has accumulated to indicate that the occurrence of unsaturated lactone rings in many active natural products, is intimately connected with the pharmacological and anti biotic activity of these substances (McCawley, Rubin and Giacomino, *Fed Proc* 5 191, 1946 )

In a study of the toxic mechanisms of such lactones on cats, the reactions having been recorded on an ink writing oscillograph, it has become evident that early physiologic effects and the ultimate toxic mechanism depend not only on the presence or absence of unsaturation, but also on the actual position of the unsaturated bonding in isomeric compounds

Acute toxicity studies in mice showed the angelica lactones (Winthrop Chemical Company and Calco Chemical Company), i e , the isomeric

<sup>1</sup> Supported by a Fluid Research Fund Grant Yale University School of Medicine

<sup>2</sup> National Institute of Health Research Fellow in Pharmacology

2-pentene-1,4-olide and 3-pentene-1,4-olide, to have a wide range of LD<sub>50</sub> when injected into the abdominal cavity. 2-pentene-1,4-olide, 215 mg/kg, 3-pentene-1,4-olide, 800 mg/kg. Both compounds increased the respiratory rate of the cat two to three-fold and death was presumably due to respiratory failure, although the 3-pentene-1,4-olide ultimately produced generalized clonic convulsions ending in complete exhaustion. With both compounds, there was evidence of initial cortical stimulation and final cortical depression. The 3-pentene-1,4-olide produced the most pronounced changes in the EKG, namely, a two-fold increase in amplitude of the QRS complex initially with an ultimate decrease in its amplitude at the toxic level. The lethal dose for the cat by intravenous injection was 500 mg/kg for 2-pentene-1,4-olide, and 1000 mg/kg for 3-pentene-1,4-olide.

The saturated analog studied, butyrolactone (Cliffs Dow Chemical Company) demonstrated at one-half the lethal dose (545 mg/kg) complete depression of cortical activity. Death was due to respiratory failure, the rate of respiration having been slowed to one-half the initial rate at 300 mg/kg. EKG changes were negligible.

**On the curious pharmacology of hydrastis**  
O S GIBBS *Gibbs Laby, Memphis, Tenn.* Extract of hydrastis contains berberine and hydrastine as major quantitative ingredients. The chloride of berberine, a highly fluorescent alkaloid with dyeing properties, is less soluble than the base in consequence it precipitates in the presence of free chloride. Coupled with its dyeing properties salt causes berberine to localize in wounds, damaged tissues and certain organs, a phenomenon readily observed by the dark-light. The salt localizing action is analogous to that of silver. As berberine is a general antiseptic its old and continued use on eyes and other surfaces as an anti-catarrrhal agent receives somewhat unusual support.

Berberine on the rat's uterus causes a slow diminution of tone, amplitude, rate and response to acetyl choline. Its action appears more powerful and lasting against the extrinsic than the intrinsic motor control, but both are affected. Following berberine acetyl choline produces a tonic type of reaction.

Hydrastine increases the rate of uterine contraction in rats, with decreasing tone and amplitude. These effects, as with berberine are slowly developed. Following hydrastine acetyl choline produces an increase of contraction speed sometimes to a remarkable amount. It is accompanied by tonic contraction which is of short duration. Following berberine, but in the presence of apparently normal contractions, hydrastine immediately and powerfully reverses the tonic action of acetyl choline. This effect is readily repeatable on the

same preparation. Berberine and hydrastine together produce a rapid decrease in tone and amplitude akin to that produced by a liquid extract of hydrastis.

The striking reversal action of hydrastine in the presence of berberine has not seemingly been previously recorded and offers explanation of the empirical but wide therapeutic use of extract of hydrastis, commonly supposed to be a uterine stimulant, as a uterine sedative.

Other drugs also have the property of causing this hydrastine reversal as will be recorded later.

**Effect of theobromine derivatives and allovan on muscle metabolism**  
CHALMERS L GEMMILL  
*Dept of Pharmacology, School of Medicine, Univ of Virginia* The effect of numerous theobromine derivatives with substitutions in the one position was studied on the anaerobic glycolytic activity of extracts of muscle of the frog and on the oxygen uptake of the isolated diaphragm of the rat. Anaerobic glycolysis of glycogen to lactic acid was measured by the production of carbon dioxide from bicarbonate using Warburg vessels and manometers. The results of the theobromine derivatives on glycogen glycolysis could be divided into three groups: (1) giving a primary stimulation followed by a secondary inhibition, (2) giving inhibition, (3) giving neither stimulation nor inhibition. In the first group are methyl (caffeine), ethyl, iso amyl, propyl, crotyl, methoxyethyl and allyl, in the second group is butyl and in the third group methallyl theobromine. Theophylline, urethane and 2-aminopyrimidine have no effect on the rate of glycogen glycolysis. Allovan inhibited the production of carbon dioxide under the conditions of these experiments. The degree of inhibition is proportional to the concentration of allovan. The addition of cysteine reversed the inhibition. In contrast to the different effects of the various theobromine derivatives on anaerobic glycolysis, was the stimulation of oxygen consumption in the isolated diaphragm of the rat. All of the theobromine derivatives gave an increase in oxygen consumption when compared to the control experiments. [This work was supported in part by a grant from Eli Lilly and Company.]

**Convulsant and cardiac actions of red squill**  
HARRY GOLD, WALTER MODELL and McKEEN CATTELL  
*Dept of Pharmacology of Cornell Univ Medical College, and Cardiac Services of Beth Israel Hospital and Hospital for Joint Diseases, New York* Experiments with scilliroside, a highly purified red squill principle, indicate that, contrary to the prevailing view, the convulsant action of red squill in the rat is a function of its cardiac glycoside. After a long latent period, intravenous doses of the order of 1 mg of scilliroside give rise to prolonged convulsions which are often fatal. Doses of 2 mg or more exert a cardiac action



which may cause death with cardiac arrest in a few minutes

In the frog, scilliroside produces typical digitilis like effects with systolic standstill of the ventricle. In the cat, the effects of scilliroside on blood pressure, electrocardiogram, and force of contraction of the isolated papillary muscle are typical of digitilis bodies. In human subjects, intravenous doses produce effects similar to those after comparable doses of other digitilis glycosides, slowing of the ventricular rate in auricular fibrillation and depression of the T-wave of the electrocardiogram.

The identity of the cardiac and the convulsant principles of red squill receives support from an experiment showing that another extract of red squill, urguim, which had one half the potency of scilliroside by the cardiac action in the cat was also one half as potent by the convulsant action in the rat. It is further supported by the observation that, while not as well developed as in the case of scilliroside, nor equally developed in all, other highly purified digitilis glycosides (scilligenin, digitoxin, "gitalin," folinerin, ouabain) also possess a convulsant action for the rat [If not done under a United States Public Health Service research grant.]

On the neurological effect of some chlorinated tertiary amines ABRAHAM GOLDIN (introduced by Stephen Krop) *Medical Division, Edgewood Arsenal, Maryland, Motion Picture Demonstration*. Beta chloroethyl morpholine and beta chloroethyl dimethyl amine induce a neurological syndrome in albino mice which resembles the behaviour of Waltzer and Shaker strains of mice. Rats, cats, and dogs are somewhat similarly affected. The symptoms appear within twenty four hours after intraperitoneal injection, and persist for at least two months. The behaviour of mice after a single injection is illustrated in a ten (10) minute motion picture film. General hyperactivity, bobbing of the head, general incoordination, and a tendency to run in close circles is demonstrated both at normal camera speed, and in slow motion, and is compared with the behaviour of normal mice. The abnormal swimming pattern of treated mice is compared with that of control mice. The inability of treated mice to maintain balance on narrow footing is likewise demonstrated. This symptom pattern is not elicited by beta-hydroxyethyl morpholine or by morpholine. The effects of related compounds and the possible mechanism of induction of the symptoms are under investigation.

The antibiotic properties of a bismuth "aspergillie acid" complex ANDRES GOTH (introduced by Arthur Grollman) *Dept of Physiology and Pharmacology, Southwestern Medical College, Dallas, Texas*. While studying the effect of various metals on "aspergillie acid" it was found that

bismuth caused a marked potentiation of its antibiotic activity (A. Goth, *Science* 104: 330, 1946). Further studies indicated that bismuth and "aspergillie acid" form a complex which has a much greater antibiotic activity than the sum of the activities of its components.

The bismuth "aspergillie acid" complex has been obtained in crystalline form and an elemental analysis indicates that it contains 20% bismuth. It is very slightly soluble in water and very soluble in methyl alcohol and propylene glycol. Its activity per mg. is 15-20 times greater than that of "aspergillie acid" against *Staphylococcus aureus*, *Pneumococcus*, *M. tuberculosis* (rapidly growing strain), *Brucella melitensis*. Whereas the minimal growth inhibitory concentration of "aspergillie acid" against *Staphylococcus aureus* is 1:50,000, that of the bismuth "aspergillie acid" complex is 1:1,000,000. Gram negative bacilli, such as *Salmonella*, *Shigella* and *Eberthella typhosa* require 5 times greater concentrations for complete growth inhibition.

The MLD of bismuth "aspergillie acid" in propylene glycol given intramuscularly to mice exceeds 500 mg. per kg. Since the complex precipitates in the muscle, no direct comparisons can be made between the acute toxicity of the complex and that of "aspergillie acid" [Aided by a grant from Eli Lilly and Company.]

Responses to benzedrine sulfate—1,467 Cases D. M. GREEN *School of Medicine, Univ. of Washington*. Six hundred ninety healthy subjects received 10 mg. of benzedrine sulfate at noon on a normal working day. Responses were compared with those of 732 individuals given 325 mg. of acetyl salicylic acid. Lessened fatigability was reported by 22.6 per cent, increased efficiency by 16.4 per cent of the test group. Corresponding values for the controls were 7.6 per cent and 4.8 per cent. Restlessness, depression, dizziness and excitement were complained of with significantly greater frequency by the test group. Incidence of headache, delayed fatigue and palpitation was similar in both.

Responses to benzedrine were then determined for 777 individuals following a 14 hour working period during which the subjects were exposed continuously to great psychic stress. Half the group (360 subjects) received 5 mg. of the drug at the mid point of the period. The remainder received an additional 5 mg. two hours before the period's end. In both groups the incidence of desirable effects increased and the frequency of side reactions diminished, compared with values obtained on a normal day. These changes were most marked in the group which received two consecutive doses. 55.9 per cent of whom reported increased efficiency and 34.3 per cent, lessened

fatigability Incidence of side reactions in this group diminished almost to the vanishing point

The results suggest that effects of drugs whose actions are predominantly in psychomotor or psychosensory spheres depend not alone on the subject's physiologic and psychologic status, but also on the degree of introspection allowed by the circumstances under which the drug is administered

**The action of di-isopropylfluorophosphate on the caliber of the bronchial tree in isolated lungs** R E GREEN (by invitation), ELIZABETH A MCKAY (by invitation), and STEPHEN KROP *Pharmacology Section, Edgewood Arsenal, Maryland* Symptoms suggesting bronchiolar spasm (e g, labored respiration) are a prominent feature of acute poisoning by di-isopropyl fluoro-phosphate in experimental animals Isolated lungs of rats and rabbits perfused via the trachea with Ringer-Locke's solution were utilized to determine whether this compound possesses bronchoconstrictor power, and if so whether such an effect is demonstrable with quantities of the substance consistent with its toxicity in the intact animal Furthermore, its action has been compared with that of physostigmine and prostigmine The effect of all three compounds upon the broncho constrictor action of acetylcholine has also been studied Amounts of di-isopropyl fluorophosphate lying between 0.1 and 1.0 mg were found to be necessary to produce an appreciable increase in resistance to perfusion in the rat lung, the amounts of physostigmine and prostigmine necessary to produce comparable effects were somewhat higher The rabbit lung is much less sensitive Moreover, amounts of di-isopropyl fluorophosphate insufficient to cause bronchoconstriction per se markedly enhanced and prolonged the effect of acetylcholine All effects were reversed by small quantities of atropine permanently, and by epinephrine temporarily

It is concluded, therefore, that di-isopropyl fluorophosphate may cause bronchoconstriction in toxic doses in the intact animal via its known property of inhibiting cholinesterase and thereby sensitizing the bronchial musculature to circulating or tissue acetylcholine

**Chronic toxicity studies of 1-amino-1-phthalidylpropane hydrochloride and its effects upon blood pressure and respiration** CHARLES M GRUBER, ALBERT M LURTON (by invitation) and THOMAS M SCOTT (by invitation) *From the Depts of Pharmacology and Pathology, Jefferson Medical College, Philadelphia, Penna* One-amino 1 phthalidylpropane hydrochloride was synthesized by Ulliot and his associates who describe the pain threshold raising actions of these racemates were studied by Fellows and his associates

In our toxicity studies one group of dogs were given daily doses of either 100 mg/kg orally or 50 mg/kg intravenously of racemate A and another group B Throughout the experimental period of several weeks, the phenolsulphonphthalein and bromsulphthalein excretions, blood hemoglobin, hematocrit readings, and the erythrocyte reticulocyte and leukocyte counts remained within the variations normally observed in dogs

In the blood of seven of the fourteen dogs used nucleated red blood cells were found before the drug was given and in eleven at some time during the experimental period, but these cells appear to be normally present and not due to the drug

Microscopic and gross examinations of most body tissues revealed nothing abnormal attributable to the chemical

Both racemate A and B when injected intravenously in decerebrated cats and anesthetized cats and dogs in small doses slow respiration, but cause complete inhibition of respiration in expiration in large doses

In cats the average percentile falls in blood pressure in doses of 10, 25, 50 and 100 mg/kg were for B, 18, 31, 35, 50 and for A, 27, 44, 57, and 60 respectively In dogs racemate A in doses of 25, 50 and 100 mg/kg caused average percentile decreases of 32, 43 and 62 respectively and for B in 50 and 100 mg/kg they were 33 and 56 respectively

**Pharmacologic observations on 1,1-diphenyl-1-(dimethyl-aminoisopropyl)-butanone-2** H B HAAG, J K FINNEGAN (by invitation) and P S LARSON *Dept of Pharmacology, Medical College of Virginia, Richmond* In view of the potent analgesic action of this compound we have begun studies seeking to compare its pharmacologic properties with those of morphine For brevity the compound will be referred to below by its German name of "Amidone"

Acute toxicity studies on rats gave the following LD<sub>50</sub> values (mg per kg) for Amidone HCl oral 95 ± 33 subcutaneous, 100 ± 19, intravenous 92 ± 0.4 Comparative values for morphine sulfate were oral, 905 ± 144, subcutaneous, 572 ± 6, intravenous, 237 ± 6

Studies on the blood sugar elevating properties of Amidone HCl and morphine sulfate made on dogs showed Amidone to be about as potent as morphine as a hyperglycemic agent The dose level employed for each compound was 5 mg per kg subcutaneously

Studies on the comparative effects of chronic administration of these substances to rats and dogs are in progress

**Effect of five drugs on coronary blood flow in the dog** JOSEPH H HAFKENSCHIEL and JAMES E ECKENHOFF (introduced by Carl F Schmidt) *Dept of Pharmacology and Harrison Dept of*

*Surgical Research, Univ of Pennsylvania, and Dept of Anesthesiology, Hospital of the Univ of Pennsylvania, Philadelphia* The coronary action of papaverine, theophylline ethylene diamine, nitroglycerine, amyl nitrite, and nikethamide has been investigated utilizing a method previously described (*Am J Med Sci* **112** 123, 1916)

Papaverine and theophylline ethylene diamine were the only drugs studied which consistently resulted in an increase in coronary flow, whether injected intra arterially or intravenously Nitroglycerine proved to be a potent coronary dilator when given intra arterially but when administered systemically the response was variable Amyl nitrite also led to inconsistent responses but frequently augmented coronary flow in spite of considerable decreases in blood pressure The action of nikethamide was insignificant in all respects

Our data indicate that inferences concerning therapeutic value cannot properly be drawn from a demonstration that a drug increases coronary flow in heart-lung or other perfusion preparations To assume it obtains its therapeutic effect by this means is unwarranted Under the conditions of our experiments coronary flow can be increased by any one or more of the following factors (1) Increase in cardiac work (2) Decrease in cardiac efficiency (3) Increase in cardiac output (4) Increase in blood pressure (5) Increase in heart rate (6) Decrease in blood pH (7) Decrease in arterial oxygen content Furthermore a decrease in cardiac work or an increase in cardiac efficiency, by decreasing the heart's demand for oxygen, can make more oxygen available without increasing coronary flow

Therefore we conclude that an increase in coronary flow alone is not a valid criterion for evaluating drug action but that an attempt should be made to study all of the other factors involved, particularly cardiac oxygen consumption and cardiac efficiency Perhaps a better index for determining the therapeutic value of such a drug would be a relationship between oxygen delivery and oxygen demand

**Toxicological properties of hexaethyl tetraphosphate**<sup>1</sup> ERNEST C HAGAN and GEOFFREY WOODWARD (introduced by Bert J Vos) *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C* The compound known in Germany as "Bladan" and introduced in this country as "hexaethyl tetraphosphate" (HETP) has been recommended as an insecticide for aphids, red spiders, citrus mites, etc Investigation of its toxicological properties seemed desirable

The oral acute LD 50 for mice was found to be 55.5 mg/kg, for rats 7.0, for guinea pigs 16.0, and for rabbits 20.5 The intravenous LD 50 for rabbits was found to be 0.69 mg/kg A difference in sex susceptibility was noted in rats Application of the determined LD 50 gave Females, 14/20, Males, 2/20 Poisoned animals exhibited fibrillary twitchings, pin-point pupils, salivation, and lacrimation, regardless of the route of administration Deaths usually occurred within 24 hours Application of 0.5% solution of HETP in propylene glycol to eyes of rabbits produced within a few minutes miosis which persisted about 4 hours Because of the similarity of the symptoms to those observed in animals poisoned by eserine, it was thought that the action of HETP was due to its interference with cholinesterase

It was found that prior administration of eserine would protect animals against lethal doses Intravenous administration to rabbits of 1.26 mg/kg of HETP killed 16/16 In previously eserinized rabbits (0.125 mg/kg) the mortality ratio was only 2/13 A similar observation was made in rats given HETP orally and eserine intraperitoneally Eserine exhibits a similar protective action against diisopropylfluorophosphate

Experimental study of the anthelmintic value of the cyanine drugs in dogs DONALD R HALES and ARNOLD D WELCH *Dept of Pharmacology, School of Medicine Western Reserve Univ, Cleveland Ohio* The striking antischistosomal activity of cyanine compounds led to a study of their anthelmintic activity in the dog

Of the compounds tested, (6 dimethylamino-1 methyl 2 quinoline) (2,5 dimethyl-1 phenyl 3-pyrrole) dimethinecyanine chloride (CMR Center No 715) exerted the most marked anthelmintic activity against ascarids (*Toxocara canis* and *Toxascaris leonina*) hookworms (*Ancylostoma caninum*), and whipworms (*Trichuris vulpis*)

A single oral dose of 20 mg/kg, was vermifugal for all ascarids in 11 of 12 dogs harboring *Toxocara canis* or *Toxascaris leonina*, in the remaining dog only one of five worms was expelled

At various oral dosage levels administered over varying intervals of time, #715 killed all hookworms in 15 of 24 dogs, while the vermifugal effectiveness in the remaining dogs varied from 36 to 89 per cent A single dose of 20 mg/kg was sometimes completely effective, in other cases, expulsion was incomplete even with repeated dosage

Complete removal of *Trichuris vulpis* was accomplished in 8 of 23 dogs, but only after repeated dosage, usually at a level of 20 mg/kg, at intervals of 8 to 24 hours No chemotherapeutic effectiveness has been noted against *Dipylidium caninum*

A toxic manifestation of the drug was a temporary anorexia In about 30 per cent of dogs, oc-

<sup>1</sup> A portion of the funds used in this investigation was supplied by a transfer recommended by the Office of the Surgeon General War Department to the Division of Pharmacology of the Food and Drug Administration

per day, was established by giving ground Purina Fox Chow ad lib. The reduced caloric intake consisted of 50% of the normal.

All rats treated with Pyribenzamine received 3 mg/kg/day for six weeks. Weights were recorded weekly and blood studies were made periodically for determining the values of the hematocrit, RBC, WBC and differentials of the latter.

**Results** By the end of the first week all rats on the reduced diet showed a decrease in body weight and WBC with little change in hematocrit or RBC values while those on the normal diet remained unchanged. By the end of six weeks there was a 50% reduction in body weight and WBC in Groups II, III and IV, but again no change in Group I. It would seem, therefore, that this type of experimental leucopenic animal resulting from a reduced caloric intake is not more vulnerable to the toxic effects of relatively high doses of medications, in this instance Pyribenzamine, when administered for seven weeks, this statement may lend itself to alteration after further study of this type of animal under other forms of medical therapy.

**Observations on the effects of benzyl-imidazoline (priscol) in man** JAMES P. HENDRIX, M. J. REARDON (by invitation) and F. A. MARZONI (by invitation) *Depts. of Medicine and Surgery, Duke Univ. School of Medicine, Durham, N. C.* Priscol is known to possess adrenolytic and sympatholytic actions. Following experiments in dogs (Marzoni et al, accompanying abstract) priscol was administered to patients. Its effects were observed on blood pressure, heart rate, skin temperature, pressor response to expiratory breath holding or cold, and on the response to 5-15 gamma of epinephrine i.v.

When priscol is injected i.m. or i.v. in increasing dosage during an experimental period of about one hour, effects develop in approximately the following order: flushing of the skin over the face and upper trunk, gradual warming of the extremities with decrease in skin temperature gradient from trunk to distal phalanx, increase of 10-20 beats/min in heart rate, slight rise or fall in B.P. (recumbent), increased piloerector activity with temporary tingling and chilliness, diminution, loss or reversal of response to epinephrine, increased peristalsis, postural hypotension, muscle twitching, diminution or loss of response to pressor reflexes mentioned. Reflex dilatation of the pupil is not inhibited. Oral administration also is effective.

Increase in peripheral skin temperature is well marked in normals and patients with vasospastic states. It usually is present (but not maximal) at doses (0.5-1.0 mg/kg) smaller than are required for adrenolysis or sympatholysis (2-3.5 + mg/kg). This suggests a vasodilating action independent of

sympathetic block. The flush resembles that produced by histamine (beta-imidazolyl ethylamine) and it is known that priscol resembles histamine in its effect on gastric acidity. Hence it is suggested that priscol has a dual vasodilating action, histamine-like effect on small vessels, and block of augmentor sympathetic vascular receptors. [Aided by a grant from Ciba Pharmaceutical Products, Inc.]

**An accurate colorimetric method for the determination of methanol in blood, tissues, and the expired air** C. H. HINE, T. E. SHEA, JR., and W. R. ALSDOFF, (introduced by F. L. Kozelka) *National Naval Medical Center, Naval Medical Research Inst., Pharmacology and Toxicology Facility*. The method is based on the acid dichromate oxidation of methanol with colorimetric estimation of the colored chromate formed. Separation of methanol from the tissues is obtained by steam distillation employing the apparatus of Kozelka and Hine. If only small amounts of blood (0.1 to 0.5 cc) are available the methanol level may be more easily determined by aeration of the vapors directly into the oxidizing reagent. Expired air likewise may be carried by a stream of ambient air into the reaction mixture and the methanol determined directly. When the optical density of the chromate is measured with a Coleman spectrophotometer at 585 $\mu$  there is little interference by the unreacted dichromate. Since the chromate-dichromate system is composed of two colored components, a correction for the diminishing amount of dichromate must be made in order that a linear relationship may be maintained. The concentration of the oxidizing reagents, the temperature and time of oxidation must be controlled carefully in order to oxidize methanol quantitatively. When methanol is added to tissues in vitro or introduced into the expired air it may be recovered in the amount of 97 per cent or more over a wide range of values (0.5 to 1000 mg). When dealing with smaller amounts of methanol (0.1 to 0.4 mg) in blood, modifications of the method will give recoveries in the order of  $\pm$  0.01 mg.

**Observations on the pharmacology of aliphatic aldehydes** PHILIP HITCHCOCK, *Dept. of Physiology & Pharmacology, Medical College of Alabama, Birmingham*. The present report is an extension of a previous note on the pharmacology of acetaldehyde (E. E. Nelson, *Proc. Soc. Exper. Biol. and Med.* 52: 23-4, 1943). The immediately adjacent members of the homologous series of aliphatic aldehydes have been examined for action on the dog's blood pressure after dial anesthesia. In contrast to acetaldehyde, formaldehyde rapidly lowers the blood pressure. The effect is rather prolonged, lasting for some minutes. Large doses (greater than approximately 100 mg/kg) are

lethal, death apparently resulting from cardiac arrest. The marked fall in blood pressure may be reversed equally well by acetaldehyde or epinephrine at the usual pressor dose levels. Repeated doses of formaldehyde cause a slow fall in blood pressure which is maintained. However, neither potentiation nor inhibition of the pressor action of acetaldehyde or epinephrine is detectable.

The members of the series beyond acetaldehyde are uniformly pressor up through those possessing fewer than six carbon atoms. Higher members of the series are depressor, so far as has been examined.

On a molar basis, propionaldehyde is about as potent as acetaldehyde. The butyraldehydes and valeraldehydes are successively less potent. Moreover, branching of the chain as in iso-butyraldehyde and iso-valeraldehyde greatly reduces the pressor activity as compared with the normal isomer.

The corresponding ketones in the aliphatic series and both aldehydes and ketones in the aromatic series are, so far as examined, depressor, and are much less potent on a molar basis than formaldehyde.

**Mechanism of uranium poisoning.** HAROLD C. HODGE, ALEXANDER DOUNCE, J. H. WILLS, T. H. LAN, PAUL FANTA and G. H. TISHKOFF (introduced by Raymond M. Bieter). *Division of Pharmacology and Toxicology, Dept. of Radiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* It is probable that by inhalation exposure only hexavalent uranium can be absorbed into the blood. Soluble tetravalent uranium compounds may be oxidized in the air or in the lung.

From physicochemical and enzymes studies it was deduced that hexavalent uranium is innocuous when complexed with substances such as bicarbonate, protein, or organic acids, and that only the uncomplexed uranyl ion (or similar ion) is toxic.

Hexavalent uranium is present in blood, chiefly in the plasma, as the bicarbonate, protein, and other complexes. The distribution between protein and bicarbonate depends upon the  $\text{CO}_2$ -combining power of the plasma, at normal  $\text{CO}_2$ -combining capacity the distribution is roughly equal. The equilibrium between the two complexes is established rapidly.

The bicarbonate complex is filtered by the glomerulus, resulting in a continual shift of hexavalent uranium from protein to bicarbonate in the plasma. Hexavalent uranium which is not excreted deposits harmlessly in the bone.

The uranyl bicarbonate complex decomposes in the proximal convoluted tubules because of the resorption of bicarbonate, establishment of a new uranyl bicarbonate-uranyl protein equilibrium,

and resorption of water. Considerable uranium becomes complexed, presumably with protein, on the tubular cell surfaces. This results eventually in injury or death to the cells, with the release of intracellular constituents including catalase and phosphatase. Recovery or death follows in two to three weeks depending upon how widespread the damage becomes.

Usually considerable amounts of uranium are excreted in the urine, having been complexed with organic acids in the tubules.

**The conversion of  $-\text{CN}$  to  $-\text{CNS}$  in dogs.** R. G. HORTON, R. E. WESTON, J. P. SAUNDERS and G. HAMMON (introduced by Stephen Krop). *Toxicology Section, Medical Division, Edgewood Arsenal, Maryland.* At intervals subsequent to the rapid injection of  $\text{LD}_{50}$  doses of  $\text{NaCN}$  into the femoral vein of dogs weighing about 20 kg, the  $-\text{CN}$  and  $-\text{CNS}$  content of blood obtained from a hepatic vein branch by catheterization through the jugular vein were compared with the contents in blood from the femoral artery and vein. Determinations of  $-\text{CN}$  and  $-\text{CNS}$  were made by the Aldridge-Evans methods.

Initially, in general, hepatic blood had the highest  $-\text{CNS}$  content, while femoral vein blood had the lowest  $-\text{CN}$  and  $-\text{CNS}$  contents. As  $-\text{CN}$  blood levels decreased and  $-\text{CNS}$  levels approached a peak, all three samples more nearly approximated each other. The rate of appearance of  $-\text{CNS}$  (expressed as  $-\text{CN}$ ) was 0.02 gamma/ml/min  $\pm$  0.01 (S.D.) regardless of whether injection was made rapidly or for some hours.

For the present data to be comparable with the  $-\text{CN}$  detoxication rate of 9.0 gamma/kg/min estimated previously (R. G. Horton, unpublished) (from the mortality of dogs following continuous injection at various rates) the  $-\text{CNS}$  would have to be distributed in 45% of the body weight. Since the  $-\text{CNS}$  is generally considered to be distributed in only 38% of the body weight, it is likely that some  $-\text{CN}$  disappears without prior conversion to  $-\text{CNS}$ —for example, through the lungs.

**On the metabolism of paludrine in the rat.** HETTIE B. HUGHES (by invitation) and L. H. SCHMIDT. *Crist Hospital Inst. of Medical Research, Cincinnati, Ohio.* Balance studies were carried out in rats receiving paludrine. Groups of animals were given daily doses of this drug of 25 and 50 mg per kg for a period of 14 days, one half the daily dose being administered every 12 hours. Feces and urine were collected separately each day and analyzed for paludrine content. The daily urinary output of paludrine averaged 2.5 per cent of the dose ingested in animals receiving 25 mg per kg and 4.6 per cent in rats receiving 50 mg per kg. The daily fecal output of paludrine averaged 34 and 28 per cent of ingested drug on the 25 and 50 mg dose levels respectively. Thus, no

otherwise, vomiting and lower levels of methemoglobin resulted with recovery within 15 hours

Oral or intravenous administration of ketosuccinic acid change these results (1) maximum levels of methemoglobin were 15 per cent below those of controls, (2) methemoglobin concentration subsequently dropped to 50 per cent of total hemoglobin, and (3) the dogs lived for about 5 hours longer than the controls

Motor and sensory paralysis were other phenomena noted with the first signs appearing within an hour in both controls and ketosuccinate medicated dogs In 3 hours complete surgical anesthesia, muscular relaxation and loss of reflexes occurred Blood pressure remained normal, cholinergic responses were unaffected, but adrenergic responses—inhibited The CNS effects which appeared at low methemoglobin levels (about 45 per cent) were not reversed by ketosuccinate and, therefore, are probably independent of methemoglobinemia

**Absorption and diffusion of ethyl alcohol from the stomach of the rat** LEONARD KAREL and JOSEPH H FLEISHER (introduced by Stephen Krop) *Toxicology Section, Medical Division, Edgewood Arsenal, Maryland* By modifications in the Widmark and Nicloux methods, the following observations were made on gastric absorption and diffusion in rats at the end of 15 minutes following the injection into the stomach of 1.13 grams/kg of alcohol

- (1) Preliminary results indicate that absorption and diffusion are somewhat dependent on "filtration" pressure, since the blood level of alcohol and the quantity diffusing is less when the stomach is cannulated than when it is ligated at cardia and pylorus
- (2) In 15 minutes, an appreciable diffusion occurs through the walls of the ligated, excised stomach
- (3) When the doubly ligated, otherwise intact, stomach is exteriorized on the sutured abdomen, alcohol diffuses through the gastric walls while absorption, determined by blood levels, is proceeding
- (4) When the ligated stomach is enclosed in the abdomen, blood levels are higher than in (3)
- (5) Preliminary experiments suggest that when the injected, ligated stomach is allowed to remain in the open peritoneal cavity, diffusion and blood values are intermediate between those in (3) and (4), thereby indicating that the alcohol which diffused through the gastric walls was absorbed from the peritoneal cavity
- (6) Fifteen minutes following the introduction of 1.13 gram of alcohol per kg, approximately 62 per cent of the injected alcohol was found in the gastric contents, 7.7 per cent in the gastric walls, and 0.24 per cent in the expired breath The remainder is presumed to have been

absorbed, since blood levels were positive—mean = 91.6 mg per cent

**The intraperitoneal toxicity of some glycols, glycol ethers, glycol esters, and phthalates in mice** LEONARD KAREL, BENJAMIN H LANDING and THOMAS S HARVEY (introduced by Stephen Krop) *Toxicology and Pathology Sections, Medical Division, Edgewood Arsenal, Maryland* The acute, intraperitoneal median lethal doses for 16 solvents belonging to the glycol, glycol ether, glycol ester, and phthalate series were determined in Carworth Farms, female, albino mice, which were observed for 7 days following injection The LD<sub>50</sub>'s, in millimoles per kg, and the pathological changes observed with some of the solvents up to 72 hours were as follows: *propylene glycol* (127.87), *diethylene glycol* (91.69), *ethylene glycol* (90.55), *triethylene glycol* (54.27)—toxic reaction in spleen and thymus, renal glomerular and tubular damage, high white count, pulmonary congestion, and atelectasis, *dipropylene glycol* (33.54)—renal tubular degeneration, *ethyl carbitol* (29.14)—toxic reaction in spleen, renal glomerular and tubular degeneration, *methyl cellosolve* (28.25)—toxic reaction in spleen and lymph nodes, renal tubular degeneration, *ethyl cellosolve* (18.97), *dimethyl phthalate* (18.75)—pulmonary congestion and atelectasis, toxic reaction in spleen and lymph nodes, renal tubular necrosis, *diethyl phthalate* (14.87)—pulmonary congestion, edema, and petechial hemorrhage, toxic reaction in spleen, renal tubular degeneration, *ethylene glycol monoacetate* (13.93)—pulmonary congestion and atelectasis, *diethyl phthalate* (12.37)—pulmonary congestion, edema, and petechial hemorrhage, toxic reaction in spleen, and renal tubular degeneration, *dioxane* (8.97), *glycol diacetate* (8.14)—pulmonary congestion, renal tubular degeneration, *butyl carbitol* (5.24)—pulmonary congestion and atelectasis, toxic reaction in spleen and lymphoid tissue, glomerular and tubular degeneration, *allyl diglycol carbonate* (0.98)—pulmonary congestion, atelectasis, and edema, toxic reaction in spleen and lymphoid tissue, congestion of viscera, marked renal tubular damage All starvation controls were negative

**Femoral arterial and venous blood nitrogen content of dogs during denitrogenation by continuous oxygen inhalation** LEONARD KAREL and RAYMOND E WESION (introduced by Stephen Krop) *Toxicology Section, Medical Division, Edgewood Arsenal, Md* The nitrogen content of femoral arterial and venous blood was determined at successive intervals up to 360 minutes in anesthetized dogs during denitrogenation by continuous inhalation of 99.6 per cent oxygen, or a 95 per cent oxygen, 5 per cent carbon dioxide mixture, through a tracheal cannula Nitrogen analyses were made by the Edwards, Scholander, and Roughton method, with occasional checks being

made by the Van Slyke or the Horvath and Roughton manometric methods

The mean values (and standard errors) obtained at 0, 10, 20, 30, 40, 60, 180, 240, 300, and 360 minutes, respectively, for arterial blood are as follows: 1.11 (0.023), 0.28 (0.019), 0.25 (0.015), 0.22 (0.014), 0.21 (0.018), 0.21 (0.012), 0.19 (0.014), 0.16 (0.016), 0.14 (0.011), and 0.12 (0.020) volumes per cent. For venous blood, the corresponding values are 1.12 (0.020), 0.45 (0.030), 0.39 (0.037), 0.34 (0.039), 0.31 (0.015), 0.27 (0.020), 0.24 (0.016), 0.20 (0.013), 0.19 (0.017), and 0.15 (0.013). Each cited value for nitrogen, with the exception of that for 360 minutes, which is the mean of only four observations, represents the average of determinations on ten different animals. An analysis of variance for the values between 60 and 360 minutes indicates a significant trend in the rate of fall of the curve even in this range.

Because of the physically dissolved nitrogen present normally in blood, extracellular, and intracellular fluid, various tissues, especially fat and muscle, and body cavities, it is unlikely that complete denitrogenation can be achieved within several hours in dogs.

**Effects of 6-dimethylamino-4,4-diphenyl-3-heptanone (Dolophine) on intestinal motility** NORMAN W. KARR (introduced by N. A. David) *Dept. of Pharmacology, Univ. of Oregon Medical School, Portland, Ore.* Laboratory and clinical investigations of meperidine hydrochloride (Demerol) indicate that it is spasmolytic to isolated intestinal strips, and that in ordinary clinical doses it does not cause constipation, though large doses apparently may do so (Curry, J. J., J. A. M. A. 133:243, 1947). Dolophine, a more recently introduced synthetic analgesic, has been shown to have antispasmodic action on isolated intestinal strips. We felt that a quantitative comparison of these two agents with morphine on propulsive activity of the intestine in intact, unanesthetized animals would be of value. The methods of D. I. Macht and N. B. Eddy were used. In ten normal rats, the carbon suspension traversed  $66.1 \pm 1.6\%$  of the distance from pylorus to anus in 60 minutes. When comparable doses of the analgesic agents were given to other groups of 10 rats 30 minutes before the test meal, the distances traversed in 60 minutes were: Demerol (20 mg/kg)  $56.7 \pm 4.6\%$ , Dolophine (2 mg/kg)  $45.9 \pm 2.6\%$ , and Morphine Sulfate  $23.6 \pm 3.4\%$ . Groups of 20 rabbits were used according to Eddy's method. The percentage of rabbits defecating in each 30 minute period was decreased during the first three or more hours following either Demerol (10 mg/kg) or Dolophine (1 mg/kg). We feel that these results indicate decreased propulsive activity of the intestine following effective analgesic doses of either Demerol or Dolophine. In comparable doses, Demerol is less

active than Dolophine in this regard, and both are less active than morphine.

**Chronic toxicity of certain anti-cholinesterase drugs** NORMAN W. KARR and I. H. PERRY (introduced by N. David) *Depts. of Pharmacology and Pathology, Univ. of California Medical School, San Francisco and Dept. of Pharmacology, Univ. of Oregon Medical School, Portland, Oregon.* The chronic toxicity in mice and dogs of three new anti-cholinesterase compounds has been compared with that of physostigmine and neostigmine by gross and microscopic post mortem examinations. The pharmacology and acute toxicity of (1) *m*-isopropyl *p*-dimethylamino-phenol-dimethyl-urethane methiodide, (2) *p*-dimethylamino-carvacrol-dimethyl-urethane methiodide, and (3) *p*-dimethylamino-thymol-dimethyl-urethane methiodide have been previously reported (Fed. Proc. 1:154, 1942; *ibid.* 5:184, 1946). Each of these three compounds, physostigmine, and neostigmine were administered hypodermically to mice daily for 15 days in doses of 0.01 mg/kg. All but compound (3) produced some vacuolization of the distal convoluted tubules in the kidney. Compounds (1) and (2) and neostigmine also produced some hyaline necrosis of the liver. White mice consuming an average dose of 2.75 mg/kg daily for 30 days in drinking water suffered pathologic changes of the liver cells, consisting of some degree of necrosis and fibrous tissue replacement in each group. Healthy female dogs given a daily dose of 0.5 mg/kg for two months, followed by a daily dose of 1.0 mg/kg for another two months, showed no detectable objective changes except for salivation and mild diarrhea after each dose, and no measurable decrease in kidney or liver function. In all cases there was increased fibrosis of the spleen and thickening of the capsule, and compounds (1) and (3) produced slight focal necrosis about the central veins of the liver. We conclude that these anti-cholinesterase drugs, including neostigmine, should be used with some caution in chronic diseases, such as myasthenia gravis, where long continued administration is necessary.

**Potassium intoxication in uremia** NORMAN M. KERTH, M.D., and HOWARD B. BURCHELL, M.D., (by invitation) *Division of Medicine, Mayo Clinic, Rochester, Minnesota.* Further observations have been made concerning the value for serum potassium among patients who have severe renal insufficiency. Although hyperkalemia is rare in uremia, fifteen patients have now been observed who had values for serum potassium in excess of 7.5 milliequivalents. The highest value recorded has been 10.5 milliequivalents. The factors which control the serum level of this cation are but poorly understood, and the major interest, at present, is the belief that hyperkalemia may be the immediate cause of the death of some



tients through the mechanism of cardiac arrest. This belief is based chiefly on the electrocardiographic changes which develop in association with progressive increments in serum potassium. These changes, beginning as a peaking of the T wave with narrowing of its base, and with higher values for potassium, marked widening of the QRS complex and absence of P waves, have become a stereotyped pattern, sufficient to indicate the diagnosis of hyperpotassemia. Since potassium salts are used as diuretic agents in chronic nephritis, two of the patients received 5 grams of potassium bicarbonate, then the values for serum potassium and electrocardiograms were studied. No untoward clinical reaction resulted, but the values for serum obtained would indicate the potential danger of the use of potassium salts in severe renal insufficiency. Necropsy of eleven of the fifteen patients was carried out, and the relatively normal myocardium found in the majority of the eleven cases is to be contrasted with the striking electrocardiographic abnormality.

The role of the liver in the detoxication of thiopental (pentothal) and certain other thiobarbiturates. A. R. KELLY (by invitation), B. J. ADAMS (by invitation) and F. E. SHIDEMAN, *Dept of Pharmacology, Univ of Michigan*. The duration of action of certain thiobarbiturates was determined following intravenous administration to rats with Eck fistulae. Pentobarbital (hepatic detoxication) and barbital (renal detoxication) served as control drugs. The mean duration of anesthesia with pentobarbital was increased 97% following operation, no significant increase occurred with barbital.

In a large series of operated animals, the anesthetic duration of intravenous thiopental sodium was increased 751% over normal controls. In similar experiments, the anesthetic effects of two other thiobarbiturates, 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid and 5-ethyl-5-isoamyl-2-thiobarbituric acid (Thioethamyl), were prolonged 432% and 309%, respectively, in operated animals.

Subtotally hepatectomized rats, in which the mean preoperative anesthetic duration had been obtained with intravenous thiopental, showed an 832% increase in mean duration of action, 24 hours postoperatively.

The results by the Eck fistula technique were compared with those obtained by the use of carbon tetrachloride to produce liver damage in mice. The duration of action of thiopental after poisoning was increased 1169%, and similar large increases were obtained for the other thiobarbiturates.

*In vitro* experiments involving the recovery of thiopental after incubation with rat liver have been initiated. Results thus far conform with the *in vivo* findings.

The evidence obtained with these four different

techniques definitely implicates the liver as the major organ of detoxication of the thiobarbiturates studied. [Supported by a grant from Parke, Davis and Company.]

Anti-curare action of certain azo dyes in the frog. C. J. KENSLEY (introduced by McKee Cattell), *Dept of Pharmacology, Cornell Univ Medical College, New York*. Congo red and related azo dyes have been reported to possess both a prophylactic and therapeutic anti-curare action in the frog against impure curare preparations. These experiments have been confirmed using Intocostrin. Congo red has also been found to decurarize frogs paralyzed with crystalline d-tubocurarine. This action of azo dyes has usually been ascribed to its colloidal properties, i.e. adsorption of curare, rather than to any direct effect.

A comparison of the decurarizing (d-tubocurarine) action of prostigmine, diisopropylfluorophosphate, and congo red in the intact frog has shown that prostigmine brings about a rapid recovery (ca. 10 minutes when injected into the ventral lymph sac) whereas the action of DFP and congo red are much slower. Preliminary experiments have shown (1) that the response of the frog rectus abdominus muscle to acetyl choline is potentiated by congo red and (2) that acetyl choline esterase activity is inhibited by congo red *in vitro*. These latter two actions suggest that the decurarizing action of congo red may be due in part to a mechanism other than the combination of curare with the colloidal azo dye molecule.

The effect of a non-curarizing dose of d-tubocurarine on the increased motor activity in mice induced by barbiturates. KAZUO K. KIMURA (by invitation) and KLAUS R. UNNA, *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12*. The motor activity of mice in suspended cages was measured by simultaneous recording of their movements on a kymograph and on an electric counter. Subanesthetic doses of Amytal or Pentothal (30-50 mg/kg, i.p.) produced excitement and reflex hyperirritability without hypnosis or respiratory depression. The general increase in motor activity appeared immediately and lasted for about 30 minutes. D-Tubocurarine chloride (D.T.C.), 0.4 mg/kg, administered subcutaneously 5 minutes after the barbiturate markedly decreased the excitement and hyperactivity. The same small dose of D.T.C. alone had no perceptible pharmacologic effect on control mice.

Larger doses of Amytal (75, 100 and 150 mg/kg, i.p.) produced definite hypnosis, loss of righting reflex and respiratory depression in the control group of mice with complete recovery of all animals in 45, 90 and 120 minutes, respectively. When D.T.C. (0.4 mg/kg, s.c.) was given 5 minutes after the injection of Amytal, the respiration became irregular, labored and almost en-

tirely diaphragmatic. Some of the animals died from respiratory arrest quite similar to that produced by lethal doses of D T C alone. The recovery time of the survivors did not differ from the control mice. The combination of D T C with Amytal killed 25%, 40% and 60% of the mice receiving 75, 100 and 150 mg/kg of Amytal, respectively.

Similar results were obtained with Pentothal (75, 100 and 150 mg/kg, i.p.) The duration of hypnosis in the mice given Pentothal alone or together with D T C was slightly longer than that produced by similar doses of Amytal.

**A comparative study of sympatholytic drugs**  
THEODORE O KING (introduced by T Koppányi) *Dept of Pharmacology and Materia Medica, Georgetown Univ, School of Medicine*. Benzylnidazoline HCl (Priscol) in doses of 10 mg/kg (by vein) produced epinephrine reversals without any latent periods. Nembutal anesthesia or atropinization did not interfere with vasomotor reversal. The reversal of nicotine pressor responses was not uniform. In addition to occasional complete reversals of nicotine pressor effects, priscol, in some instances, failed to abolish this pressor effect and, during the period of recovery from priscol, full nicotine pressor effects appeared earlier than normal epinephrine responses. The duration of action of priscol is about four hours.

Yohimbine HCl in intramuscular doses of 5 mg/kg also reversed epinephrine pressor effects even in the presence of nembutal anesthesia and atropinization but failed to reverse nicotine effects completely. The duration of action of this dose of yohimbine is about 8 hours, and full nicotine effects always appeared much earlier than normal epinephrine responses during the recovery period from yohimbine depression.

In a limited number of experiments dibenzyl- $\beta$ -chloroethylamine HCl (20 mg/kg) reversed epinephrine and nicotine completely but did not reverse the ergotamine (0.5 mg/kg) pressor effect. Ergotamine in suitable doses not only potentiates epinephrine and nicotine pressor responses in dogs under nembutal anesthesia, but it was possible to confirm a personal communication (Dr A. M. Lands of Frederick Stearns & Co.) that ergotamine actually converts the vaso-depressor response of 0.2 mg/kg of 1-(p-Hydroxyphenyl)-2-isopropylaminoethanol to a marked pressor effect. It may be added that when ergotamine fails to potentiate pressor effects of epinephrine and nicotine it also fails to reverse the depressor effect of 1-(p-Hydroxyphenyl)-2-isopropylaminoethanol.

**Clinical trial of 6-dimethylamino-4, 4-diphenyl-3-heptanone (Dolophine)** a synthetic analgesic. ANTON C KIRCHHOFF (by invitation) and NORMAN A DAVID *Depts of Pharmacology and*

*Anesthesiology, University of Oregon Medical School, Portland, Oregon*. In a preliminary clinical trial of the synthetic heptanone derivative, Dolophine, pain relief has been noted in dosages ranging from 5 mg to 15 mg given subcutaneously following its use for post partum, prepartum and post-operative pain. To date 101 patients have received a total of 525 administrations of the drug with nausea being complained of in 6 patients, diaphoresis in 4 patients, euphoria in 2 patients and respiratory depression in 1 patient. There were no withdrawal symptoms noted following cessation of administration of the drug for 18 to 20 days in some of the patients. Amounts of over 300 mg given over 9 to 18 days showed no cumulative effect. The drug did not possess any noticeable sedative or hypnotic effect. In general, based on our preliminary clinical trial of Dolophine, we feel that this new drug in the dosages used, is relatively free of undesirable side actions, while yet approximating the effective analgesic requirement.

**Prothrombin time following curarization**. ANTON C KIRCHHOFF and JOHN K UCHIYAMA (introduced by N. David) *Depts of Pharmacology and Anesthesiology, Univ of Oregon Medical School, Portland, Oregon*. A dosage of one-half unit of curare (Intocostrin) per pound was used as the curarizing dose in unanesthetized rabbits. Blood specimens were drawn from a leg vein at one hour and 24 hours following medication. In a preliminary trial the one hour specimens showed a decreased prothrombin percentage (increased time) and the 24 hour specimens an increased prothrombin percentage (decreased time). It is not known if the effects noted could be directly attributed to the curare or some other factor such as anoxemia during underventilation. Further work to verify these findings, and, if possible, to explain them is now in progress.

**Spasmolytic action of 6-dimethylamino-4, 4-diphenyl-3-heptanone (Dolophine)**, a synthetic analgesic. ANTON C KIRCHHOFF and JOHN K UCHIYAMA (introduced by N. David) *Dept of Pharmacology, Univ of Oregon Medical School, Portland, Ore*. Scott and Chen in a preliminary report on the synthetic analgesic compound 6-dimethylamino-4, 4-diphenyl-3-heptanone (Dolophine) at first thought to be 1-diphenyl-1 (dimethylaminoisopropyl) butanone-2 stated that it had an anti spasmotic effect on isolated smooth muscle (J P E T, 87: 63 (May) 1946). We have confirmed this work, using furmethide, a synthetic cholinergic type compound as the spasmotic agent. A noticeable decrease in spasm was noted with concentrations as low as 1 to 2500 Guinea pig gut was also noted to respond by relaxation. The strips were all set up in standard temperature controlled baths of Locke's solution. As with Meperid:

Hydrochloride, the spasmolytic action is best manifest after a cholinergic induced spasm

The evaluation of spasmolytic agents P K KNOEFEL *Univ of Louisville* Development of new spasmolytic agents has rested on the belief that the achievement of the desired result with atropine is necessarily attended by side-effects, and the claim that synthetic substitutes possess a greater proportion of atropine's useful powers than of its other actions Evidence for these points, with objective demonstration of the various effects, and comparative studies of different agents in the same person, was needed In human subjects, gastric motility was measured in terms of rate of emptying of gastric contents, gastric and duodenal motility was recorded with a halloon system, secretion of saliva, pulse rate, visual near-points were measured, behavior was recorded Atropine and three related synthetic agents previously studied were administered The motility of the alimentary tract has a comparatively high sensitivity to all these agents, but the margin between dosage required for this effect and side-effects is not large The potency of the synthetic spasmolytic agents in depressing motility in comparison with atropine is less than that seen in animal experiments The limiting factor in the use of the synthetic agents is their influence on the central nervous system, which they share to a high degree with atropine

Pharmacological methods in the study of overt behavior THEODORE KOPPANYI and ALEXANDER G KARCZMAR (by invitation) *Dept of Pharmacology and Materia Medica, Georgetown Univ, School of Medicine* This is the first of a series of studies on the correlation between the differentiation of the central and peripheral nervous system and specific responses to known drug actions during progressive stages of development *Amblystoma punctatum* larvae, 13 mm long, Harrison stage 44, were reared in sublethal drug solutions of concentrations given below in mols per cent, unless specified otherwise Controls in water do not move spontaneously, on stimulation they swim rapidly by means of tail movements and flexures of the trunk Clonic and tonic convulsions occurred after a 4-day latent period in  $5 \times 10^{-10}$  to  $10^{-8}$  strychnine solutions and in a considerably stronger,  $10^{-5}$ , metrazol solution Subsequent paralysis and pleurothotonus were irreversible on transfer of larvae into water Slight heterogony followed prolonged exposure to strychnine However, another central stimulant, coramine, failed to produce convulsions even in a lethal ( $3 \times 10^{-5}$ ) concentration Clonic and tonic convulsions, pleurothotonus and opisthotonus developed after a negligible latent period in  $2 \times 10^{-8}$  solution of DFP, an irreversible cholinesterase inhibitor DFP caused, also, a slight heterogony which dif-

fered from that induced by strychnine Larvae moved actively in  $2 \times 10^{-7}$  prostigmine solution, they showed clonic tail movements after 4 days, clonic and tonic convulsions after 3 weeks, and, finally, irreversible paralysis Only stronger, almost lethal concentration of nicotine ( $3 \times 10^{-7}$ ) caused paralysis within two days, without previous convulsions Larvae seemed to be little affected after 2 months in  $10^{-7}$  to  $10^{-9}$  atropine solution They were, however, convulsing within 12 hours and became irreversibly paralyzed within 72 hours in a solution containing both atropine and strychnine, each in a  $10^{-9}$  concentration

Differentiation of gluconate, glucose, calcium, and insulin effects on DDT poisoning in cats Rudolf Koster (introduced by McKeen Cattell) *Dept of Pharmacology, Cornell Univ Medical College* DDT was administered intravenously to cats in a soya lecithin-corn oil emulsion, and several drugs were tested as prophylactics, by vein Effects in the treated animals were compared with those in controls, which included the number of discrete convulsions, general severity (tremors, prostration, dyspnea), duration, and mortality Molecular equivalent doses of the first four agents were used

Calcium gluconate reduced convulsions and mortality, but not severity Sodium gluconate reduced mortality and, to a slight extent, convulsions, but not severity Gluconic acid reduced mortality, but not convulsions or severity, and increased survival time Calcium chloride reduced convulsions, but not mortality or severity Ammonium chloride slightly reduced mortality and convulsions and increased survival time, but had no effect on severity Glucose given before or after an LD33 reduced convulsions and mortality, and also severity when preceding the DDT However, glucose, in contrast to gluconic acid and its two salts, was ineffective against an LD95, except to increase survival time Insulin did not reduce convulsions or mortality when given by muscle 16-25 minutes before DDT, but increased survival time and severity When given 53-130 minutes before DDT, it reduced mortality, reduced convulsions in the fatal cases, but increased them in survivors, had no effect on duration, but increased severity only in the survivors

These data distinguish separate actions of calcium (anti-convulsant), gluconic acid (anti-lethal) and glucose (anti-convulsant plus anti-lethal plus anti-tremor) Only prophylactic glucose reduced the severity of tremors [The work described in this paper was carried out under a U S Public Health Service Grant]

The Baljet reaction and the glycosides of digitalis JOHN C KRANTZ, JR and FREDERICK K BRIN (by invitation) *Univ of Maryland School of Medicine* The biological activity and the re-

sponse of the various glycosides of digitalis purpurea has been studied. In general it was shown that digitoxin gives the most striking Baljet reaction, which compares with its active biological potency. Gitoxin and gitalin, which are less active biologically, give a diminished color reaction to a Baljet reagent. The relationship of these reactions to the chemical evaluation of digitalis is discussed.

The effect of di-isopropylfluorophosphate, diisopropylchlorophosphate, diisopropylphosphite and diisopropylphosphate on the mechanical response of striated frog muscle. STEPHEN KNOP, *Pharmacology Section, Medical Division, Edgewood Arsenal, Maryland*. Di-isopropylfluorophosphate and its chlorine analogue reduce or abolish irreversibly the mechanical response of isolated frog sartorius muscle to direct electrical stimulation. This effect is demonstrable after soaking the preparations for 5 to 10 minutes in 0.005 M or 0.01 M concentrations of either compound at room temperature (18–22°C). The response of isolated frog rectus abdominis muscle to acetylcholine is blocked by similar treatment with these compounds, but the response to potassium is retained. The cholinesterase activity of control muscles similarly treated and homogenized after washing was reduced to 5 per cent or less. Muscle preparations similarly exposed to equimolar concentrations of diisopropylphosphite and diisopropylphosphite revealed no alteration in excitability to acetylcholine, potassium or direct electrical stimulation, furthermore, muscles so treated with these compounds demonstrated no significant change in cholinesterase activity. The halogenated phosphate esters, therefore, possess "neuriform" properties demonstrable in isolated frog skeletal muscle in association with a reduction in muscle cholinesterase.

Central nervous system injury in experimental animals by betachlorethyl morpholine. STEPHEN KNOP, W. C. WESCOE, (by invitation) ABRAHAM GOLDIN (by invitation) and BENJAMIN LANDINC (by invitation). *Pharmacology Section and Experimental Pathology Section, Medical Division, Edgewood Arsenal, Maryland*. Mice and cats develop symptoms of generalized central nervous system damage of a permanent nature after percutaneous administration of betachlorethyl morpholine. Preliminary experiments indicate that dogs and albino rats are also susceptible to such injury by this compound. In general, the effects are most severe in LD<sub>50</sub> survivors, but profound symptoms may also occur after much smaller doses. The doses thus far used have ranged from 45 to 150 mg/kg intraperitoneally in mice and rats, and 15 to 60 mg/kg intravenously in cats and dogs. After a latent period of several hours, during which hyperactivity is evident, ataxia and weakness,

especially of the neck muscles, appear in mice, rats, and cats. In the latter, the latent period also includes retropulsive activity and signs of visual hallucinations. Permanent residues in mice (2 to 3 months at time of sacrifice) consist of long sustained running in circles, and in cats (3 to 4 months at time of sacrifice) consist of marked disturbances in gait and landing reflexes, and evidences of profound visual impairment. In one monkey, 30 mg/kg intravenously produced, after the latent period, extreme ataxia, when startled, the animal was thrown into violent incoordinate activity preventing walking or climbing, and resembling convulsions, there were no ocular disturbances. Complete recovery occurred in about one week.

Preliminary observations on the histopathology at various levels in the neuraxis of mice reveal early scattered ganglion cell changes, particularly in the purkinje cells. Later, patchy demyelination in the cerebrium, basal ganglia and brain stem appears. No inner ear lesions have been observed.

Some related compounds have been administered to mice. Morpholine and betahydroxyethyl morpholine do not produce these disturbances, even in large doses. However, betachlorethyl dimethyl amine in high doses produces an effect similar to betachlorethyl morpholine.

The effect of meningococcus endotoxin on the distribution of histamine between the blood and tissues of the rabbit. ERNEST KUN (introduced by Dr. E. M. K. Geiling). *Depts. of Pharmacology and Medicine, Univ. of Chicago*. Following the intravenous injection of meningococcus endotoxin in unanesthetized rabbits, a marked decrease in histamine content of the blood was observed. The blood histamine level dropped from an average of 8.6  $\gamma$ /cc to an average of 0.5  $\gamma$ /cc immediately after the injection. The histamine content of the blood remained far below the normal level until the death of the animal. When 0.3 mg/kg histamine (in form of phosphate) was injected intravenously into rabbits the blood histamine level immediately rose from 8  $\gamma$ /cc to 20  $\gamma$ /cc and showed a slow decrease to 17  $\gamma$ /cc after 10 minutes. When simultaneously meningococcus endotoxin and histamine (0.1–0.3 mg/kg) were injected the blood histamine level decreased from 7.5  $\gamma$ /cc to 4  $\gamma$ /cc within 5–10 minutes. It is believed that the decrease in blood histamine is probably due to a change in the distribution of histamine between blood and tissues. This assumption was corroborated by the finding that the tissues of animals, poisoned with meningococcus endotoxin (muscle and liver) showed a 3–4 fold higher histamine content than the normal ones.

The variation of toxicity with particle size of UO dust. CHARLES W. LABELLE (introduced by H. B. Haag). *Division of Pharmacology and*

(Lester and Greenberg, *J Pharm and Exp Therap* 81 182, June, 1944)

The anti-histamine action of pyridindene derivatives G LEHMANN EDWIN HAGAN (by invitation), GEORGE BARBAROW (by invitation) and MARGARET ROE (by invitation) *Research Labys, Hoffmann-La Roche, Inc Nutley, N J* Of several pyridindene derivatives synthesized by Drs Wenner and Plati, "THEPHORIN,"<sup>1</sup> 2-methyl-9 phenyl-tetrahydro-1 pyridindene (Nu-1504) proved to be very potent in antagonizing important physiological effects of histamine, on smooth muscle, on arterial pressure and on capillary permeability

The isolated guinea pig's ileum is not affected by 0.2  $\gamma$  histamine phosphate in the presence of 0.01  $\gamma$ /cc of Nu-1504 This inhibitory effect becomes gradually stronger if the interval between Nu-1504 and histamine administration is lengthened

0.5 mg/kg of Nu-1504 i.p. protected 50% of guinea pigs exposed to a histamine spray containing 0.4 mg histamine base per liter air, whereas only 2% of the untreated control animals survived 5 mg/kg i.p. Nu-1504 protects guinea pigs against 10-12 fatal doses of intracardially injected histamine and against death from anaphylactic shock 1 mg/kg Nu-1504 intravenously in cats prevents the occurrence of histamine induced bronchospasm recorded as by Roessler and Konzett

The vasodilator effect from intravenous histamine in anesthetized cats is either abolished or greatly diminished by Nu-1504 The same is true of the histamine induced vaso-pressor effect in decapitated cats The rise in arterial pressure often observed after large doses of histamine in urethanized rabbits is reversed after Nu-1504

In addition to its specific antihistamine action Nu-1504 also antagonizes the spasmogenic effect on smooth muscle of acetyl-choline, epinephrine and Barium ions

**Gonadotrophic potency of the pituitary of rats after desoxycorticosterone** - R C LI *Dept of Pharmacology, Peiping Union Medical College, Peiping, China* In an attempt to determine quantitatively the gonadotrophic activity of the pars distalis of the pituitary under the influence of an adrenal cortical hormone, desoxycorticosterone acetate<sup>3</sup> was injected subcutaneously to seven adult male albino rats (body weight = 249-294 gram) in daily doses of 10 mgm for 8-10 consecutive days (DP) On the day following the last injection the gonadotrophic potency of the pituitary was assayed in 21 day immature female rats

Pituitaries from litter-mate rats receiving sesame oil were used as controls (CP) The results were average paired ovarian weight =  $45.12 \pm 3.89$  and average uterine weight =  $130.3 \pm 13.0$  mgm for DP, average paired ovarian weight =  $34.03 \pm 3.34$  and average uterine weight =  $145.1 \pm 2.46$  mg for CP While the DP pituitary appeared more potent than that of CP, the difference is not considered significant ( $P = 0.05$  for ovarian weights)

**Further studies of the effects of chloroform on cardiac irregularities in the dog** ROLAND R. LIEBENOW (by invitation) and O. SIDNEY ORTH *Dept of Pharmacology, Univ of Wisconsin Medical School, Madison* Previous work indicates that the manifestations of chloroform on cardiac automaticity vary with different species Although in certain animals such as the cat the effect is one of sensitization to various stimuli, this has not been found to be predominant in dogs

Twenty young dogs used in a series of 63 administrations were anesthetized with chloroform by means of open drop, to and fro absorption, and intravenous techniques for periods ranging from one-half to one hour Continuous electrocardiographic observations were made during each anesthesia The effects of various autonomic drugs were used to determine the site of action of chloroform

In anesthetizations without premedication, as accomplished by rapid induction, cardiac arrhythmias appeared frequently The results indicated a predominant depressive phenomenon Ventricular and cardiac arrests were the most severe Ventricular tachycardia during induction occurred but once in the series Five deaths occurred during anesthesia, including one with an intravenous administration of an isotonic saline chloroform solution, all followed development of irreversible slow ventricular rhythms

Forty injections of epinephrine during anesthesia in dosages varying from 0.01 to 0.05 mg/kg produced widely different results Freedom from irregularities or depressed cardiac conductions were encountered five times more frequently than ventricular tachycardia or fibrillation Individual sensitivity difference was the outstanding factor Atropine (0.05 mg/kg) given intravenously before or during anesthesia produced no arrhythmias, when subsequent injections of epinephrine were made, more pronounced excitatory arrhythmias occurred, including two deaths by ventricular fibrillation

Sympatholytic drugs, DHE 45 and DHO 180, effectively blocked excitatory cardiac arrhythmias

**Excretion of octin, a sympathomimetic aliphatic amine** E. WILLIAM LIGON, JR., ROLLAN SWANSON and E. LEONG WAY (introduced by Paul

<sup>1</sup> U. S. Pat. Off.

<sup>2</sup> This work was completed in 1941

<sup>3</sup> Dercortin was supplied by Ciba Pharmaceutical Products Inc. N. J.

K. Smith) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* The metabolism of 6 methylamino 2-methyl-2 heptene (octin) was investigated using a modification of Brodie's methyl orange technique (*J Biol Chem* 158 705-714, 1945) sensitive to 0.5 microgram per cc of blood or urine. With single oral doses (0.12 gram octin mucate tablet equivalent to 0.069 gram free base) in six humans, 24 hour excretion varied from 6 to 37 per cent, with peak excretion in two to six hours. Administration of four grams of ammonium chloride in divided doses during the first eight hours increased the excretion in four of these six. In one individual whose excretion was high, appreciable levels were found in the urine for sixty hours. Application of Craig's eight plate separatory funnel distribution technique (*J Biol Chem* 161 321-332, 1945) to urine from two individuals revealed no difference between the distribution of apparent octin and true (added) octin.

It was found that intravenously administered octin disappeared from the blood of two rabbits and one dog much more rapidly than could be accounted for by excretion or equal distribution in all body water. Mice injected intraperitoneally 25 mg per kg, were killed after varying intervals and homogenized in 0.2 N HCl. The fluid separated by centrifuging was analyzed for octin content. Results showed that approximately two thirds of the injected amount was destroyed or very firmly bound in two to four hours. Half the remainder could be recovered from urine leaving about one sixth unaccounted for. [Aided by a grant from Bilhuber Knoll Corp.]

A method for selection of synthetic compounds which prevent excitatory responses to epinephrine. EARL R. LOEW and AUDREY MICETICH (by invitation) *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12, Illinois*. The toxicity of epinephrine in mice was reduced by compounds which block or reverse the pressor effects of epinephrine and prevent excitatory responses following stimulation of adrenergic nerves, but not by numerous other types of drugs. Yohimbine and dibenzyl  $\beta$  chloroethylamine (Dibenamine), in oral doses of 25 to 50 mg per kg, reduced the mortality rate following intraperitoneal injection of epinephrine (LD<sub>50</sub>). Potency of each active synthetic compound under investigation was expressed as the minimal effective dose which significantly reduced mortality from that obtaining in a concurrent control group of 20 mice. Onset and duration of action of each compound was determined by permitting 1 to 18 hours to elapse between drug treatment and epinephrine injection.

Striking activity was demonstrated with alkyl derivatives of benzhydryl- $\beta$  chloroethylamines,  $\alpha$  naphthylmethyl  $\beta$  chloroethylamines and 2 bi

phenoxyethyl  $\beta$  chloroethylamines. Activity was rapid in onset and of long duration. Low oral doses in mice (3.0 to 12.5 mg per kg) reduced epinephrine toxicity within one hour and the effect frequently persisted for more than 18 hours. These effective doses represent small fractions of the oral LD<sub>50</sub> in mice which ranged from 700 to 2000 mg per kg. All compounds produced some degree of local inflammatory reaction.

Active compounds selected by this pharmacological test induced "epinephrine reversal" and diminished or blocked excitatory responses following stimulation of adrenergic nerves in dogs and cats.

The development of a useful method for selecting and partially evaluating active compounds and the full cooperation of the participating chemists has provided an opportunity to correlate toxicity and pharmacological activity with chemical structure within several series of compounds. [Compounds and financial support from Parke, Davis and Company.]

Antagonism of the excitatory responses to epinephrine and adrenergic nerve stimulation with benzhydryl-alkyl- $\beta$ -chloroethylamines. EARL R. LOEW, AUDREY MICETICH (by invitation), and PAUL ACHENBACH (by invitation) *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12, Illinois*. Several benzhydryl alkyl  $\beta$ -chloroethylamines blocked and reversed the pressor action of epinephrine and prevented those excitatory responses which follow adrenergic nerve stimulation. Thus, these compounds exerted an action qualitatively similar to that demonstrated by Nickerson and Goodman (1946) for dibenzyl  $\beta$  chloroethylamine (Dibenamine).

In mice, oral administration of the benzhydryl compounds (3.0 to 12.5 mg per kg) reduced the toxicity of epinephrine injected intraperitoneally. This action was more rapid in onset and more prolonged than that exerted by Dibenamine.

Extensive studies in anesthetized cats and dogs revealed that benzhydryl ethyl  $\beta$  chloroethylamine HCl (10 mg per kg, i.v.) reversed the pressor responses to epinephrine and KCl. Excitatory effects of adrenergic nervous activity were diminished or blocked in one or two hours as indicated by diminution or absence of hypertension following faradization of the splanchnic nerve in adrenal-inactivated dogs and by a diminished degree of retraction of the contracting membrane of cuts following faradization of the cervical sympathetic nerve. After a single intravenous dose of 10 mg per kg of this ethyl homologue in unanesthetized dogs, epinephrine injections during the following 72 hours induced hypotension or failed to elicit pressor responses.

No appreciable antagonism of the depressor action of histamine or acetylcholine has been

detected Effects on adrenergic, inhibitory responses have not been sufficiently investigated A search is being made for qualitative differences in properties of various homologues in the chemical series [*Compounds and financial support from Parke, Davis and Company*]

Structure-activity relationship (SAR) and pharmacological peculiarities of new synthetic congeners of tetrahydrocannabinol S LOEWE and ROGER ADAMS (by invitation) *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City, Utah, and Noyes Chemical Lab, Univ of Illinois, Urbana, Illinois* Continued studies of the class of 1-hydroxy-3-alkyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-dibenzopyrans (3-alkyl-R) demonstrate that variations in the 3-alkyl side-chain can produce high marihuana activity SAR in this class is characterized by the following 3-n-amy-1-R has a potency (P) of 1.0, only  $\frac{1}{16}$  that of the isomeric natural charas tetrahydrocannabinol, n heptyl-R (pyraheyl, P = 2.0) represents the peak potency in the 3-n alkyl-R series The P of some branched 3 side chain isomers of pyraheyl (1-methyl-amy-1, 1,1-dimethyl-butyl, 1 ethyl-2-methyl-propyl) is between 3.0 and 4.0 However, the most potent homolog in the branched 3-(1-methyl-alkyl)-R series was that with an alkyl of eight and not six C-atoms 3-(1-methyl-octyl)-R has P = 38, i.e., more than twice the potency of the most active natural congener In some double-branched side-chain series, peak potency is also embodied in homologs with side-chains having more C-atoms than in the n-alkyl series The most active of these substances is, for the time being, 3-(1,2-dimethyl-heptyl)-R (P over 100), less than one microgram per kg elicits marked ataxia in the dog Another potentiality is indicated in 1-methyl-nonyl-R Its potency is only  $\frac{1}{16}$ th that of its next lower homolog, but its action persists for many days, whereas that of equi effective doses of its congeners lasts several hours Another peculiarity of SAR concerns the closely related 3-(1,1- and 1,2 dimethyl-heptyl)-Rs Whereas, in microgram doses, the latter displays a selective marihuana activity, it is a potent convulsant when given in the threshold dose range for ataxia of the former compound [*Assisted by grants-in-aid of research from the U S Public Health Service and from the Abbott Laboratories*]

Anticonvulsant action of marihuana-active substances S LOEWE and LOUIS S GOODMAN *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City, Utah* To elucidate further the unique neurological actions of cannabis principles and synthetic congeners, they were examined for anticonvulsant activity in rats Natural charas tetrahydrocannabinol and its synthetic 3-n-heptyl ("pyraheyl"), 3-(1-methyl-octyl) and 3-(1,2-dimethyl-heptyl) homologs were

effective in the ratio of about 7:1:80 > 200 in abolishing the hindleg tonic extensor component of maximal electroshock seizures (60 cycle AC, 150 mA, 0.2 sec, corneal electrodes) This potency ratio is rather similar to that of their ataxia potencies in the dog, thus suggesting that anticonvulsant and marihuana activity are closely related Threshold doses were below those causing ataxia and other neurological signs When tested for suppression of Metrazol convulsions, the same substances were found ineffective and exhibited a marked lethal synergism with Metrazol The pattern of high anticonvulsant potency in the maximal electroshock test and absence of protection against Metrazol aligns the marihuana congeners with the diphenylhydantoin-type of anticonvulsant Indeed, marihuana-like ataxia and catalepsy could be produced in dogs with appropriate doses of diphenylhydantoin Anticonvulsant synergism between diphenylhydantoin and marihuana active compounds could also be demonstrated [*Assisted by grants-in-aid of research from the U S Public Health Service and the Abbott Laboratories The cannabis congeners were synthesized by Professor Roger Adams*]

Studies on the parenteral administration of hydrogen peroxide ALLAN L LORINCZ and J J JACOBY (introduced by J M Coon) *Dept of Pharmacology, The Univ of Chicago* Intravenous oxygen has been used on several occasions clinically for the treatment of hypoxia and shock with reported benefit Since in human blood, catalase rapidly decomposes hydrogen peroxide into water and molecular oxygen, studies on the parenteral administration of hydrogen peroxide solution to animals were undertaken to obtain an easily controlled and convenient method for intravascular oxygen administration

Three per cent hydrogen peroxide exerted no deleterious effects on the blood of several animal species other than methemoglobin formation in those with very low catalase levels as shown by quantitative blood catalase activity determinations Intravenous hydrogen peroxide tolerance in the dog and chicken was limited by methemoglobin formation, while in the rabbit and cat by gas embolism In the cat, oxygen in the form of hydrogen peroxide could be administered intravenously at least twice as fast as in the form of oxygen gas without producing severe embolic signs

Thirty mice given maximal subcutaneous doses of hydrogen peroxide twice daily for two weeks showed no gross or histologic deleterious effects other than temporary embolic phenomena and a 25 per cent incidence of local skin ulcers

In the cat, intravenous hydrogen peroxide even in small amounts aggravated rather than reduced an existing hypoxia as shown by blood gas analyses Also, little noteworthy benefit followed the use of



intravenous hydrogen peroxide in treating carbon monoxide poisoning, hemorrhage, and chemical toxic shock.

While intravenous hydrogen peroxide has little therapeutic value in the cat, further investigation of its use in certain hypoxic and shock states in man may be indicated.

Action of chemotherapeutic agents on *Trichomonas vaginalis*, *Trichomonas hominis* and *Trichomonas foetus* in vitro. ETTA MAE MACDONALD (introduced by A. L. Tatum) Dept. of Pharmacology, Univ. of Wisconsin Medical School, Madison. Many types of treatment are recommended for trichomonas infections but no reliably efficient chemotherapeutic agents are available. Data from *in vitro* experiments on bacteria free cultures of three species, viz, *T. vaginalis*, *T. hominis* and *T. foetus*, are presented here to illustrate the effectiveness of certain classes of drugs and the relative susceptibilities of the species.

Cessation of motility of the respective trichomonads observed microscopically was used as a criterion of the relative activity of the drugs. That this may be a valid indication of depression or destruction of organisms was shown by the failure of treated organisms to survive or recover when transplanted into favorable nutrient media.

Salts of mercury are the most effective drugs against trichomonads, silver salts, formaldehyde, certain dyes, and solutions of common chemicals having high osmotic pressures also are active. Either cationic or anionic detergents effect dissolution of the organisms. Mucinous materials mixed with the organisms reduced the effectiveness of certain of the drugs more than others, some precipitated a protective layer of mucin around groups of organisms, and others greatly reduced the viscosity of the mixtures and acted promptly on the trichomonads.

*T. vaginalis* and *T. hominis* are alike in their reactions to all types of drugs employed in this test, whereas *T. foetus* is more resistant to these drugs. These results may be taken to indicate a much closer relationship between *T. vaginalis* and *T. hominis* than for either to *T. foetus*. [Aided by grants from the Wisconsin Alumni Research Foundation and the Upjohn Company.]

The effect of tetraethylammonium on the blood flow in the extremities. D. MALTON, S. W. HOOBLER, H. T. BALLANTINE, JR., R. B. NELIGH, S. A. COHEN and R. H. LYONS (introduced by G. K. Moe) Depts. of Internal Medicine, Surgery and Pharmacology, Univ. of Michigan Medical School, Ann Arbor, Michigan. Following the intravenous administration of 500 mg. of tetraethylammonium to normal subjects there is a prompt rise in blood flow in the hand and foot and to a lesser extent in the forearm as determined by the venous occlusion plethysmograph. This increase reaches a peak in

3-5 minutes, is maintained for about 5 minutes and then decreases to control levels after 30-40 minutes. The increase in blood flow occurs in the presence of a transient fall in blood pressure which quickly returns to previous levels. The increase in skin temperature reaches a maximum 10-15 minutes after injection and continues to be elevated for 50-60 minutes even though the blood flow has returned to control levels. Vasoconstriction induced by the cold pressor test is at times abolished by the drug. The response in normal subjects is not necessarily maximal since greater changes in blood flow in the feet have been observed after paravertebral block or after heat to the trunk. Usually there is no further increase in blood flow after tetraethylammonium when vasoconstrictor tone has been reduced by warming the subject. On the other hand, when a greater degree of neurogenic vasoconstriction is initially present, there is generally a greater response to the drug.

Rectal administration of penicillin. E. E. MANDEL and J. D. THAYER (introduced by F. Stegmann) U. S. Marine Hospital, Staten Island, N. Y. In view of obvious discrepancies in literature concerning rectal absorption of penicillin, both blood levels and urinary excretion of penicillin were studied in adult males following its administration either by way of a retention enema or of a suppository. The dosage was 0.5 and 1.0 million units with the exception of one case in which one hundred thousand units were given.

Absorption from a suppository appears to follow a definite pattern in that it results in the rapid attainment of greatest penicillin activity in the blood within less than thirty minutes, succeeded by a gradual decline over a period of several hours. The height of the serum level and its duration vary in proportion with the dosage employed, its maximum averaging 0.5 units per ml. with a dose of 0.5 million units, 1.0 per ml. after the use of one million units. The twenty-four hour urinary recovery averages 6%.

Penicillin absorption from a retention enema proceeds slowly and is generally inferior to that from a suppository in its effect on both serum concentrations and urinary excretion.

Streptomycin absorption from rectal suppositories, as determined by urine assay in four cases, is practically nil.

It is concluded that the therapeutic use of penicillin suppositories is too uneconomical to be recommended but that it may occasionally be of practical value in combination with other routes of administration in the home management of small children. The equivocal results in the previous literature appear to be essentially clarified by this study.

Toxicity and mechanism of action of tetraethyl pyrophosphate. GEORGE H. MANGUN (by invita-

tion) and KENNETH P. DuBois *Univ of Chicago Toxicity Lab and the Depts of Biochemistry and Pharmacology, Univ of Chicago* Tetraethyl pyrophosphate (TEPP) has been investigated and found to be a strong inhibitor of cholinesterase *in vivo* and *in vitro*. Under the conditions of test it was found to produce 50% inhibition of rat brain cholinesterase *in vitro* in a final concentration of  $4.0 \times 10^{-9}$  M is compared to  $1.6 \times 10^{-8}$  M for hexaethyl tetraphosphate and  $6.3 \times 10^{-8}$  M for diisopropyl fluorophosphate under the same conditions.

When injected intraperitoneally TEPP inhibits rat tissue cholinesterase at the LD-50 (0.65 mg/kg) as follows in terms of per cent inhibition compared to controls: Brain—20, 45, 75, 69 per cent, Submaxillary—35, 75, 75, 74 per cent, Serum—91, 88, 94, 95 per cent, Red cells—50, 74, 78, 67 per cent. The first two animals were sacrificed at 20 minutes and the last two died at 18 minutes and 17 minutes respectively.

TEPP is of interest as a rodenticide. The LD-50 by intraperitoneal injection is 0.85 mg/kg for mice and 0.65 mg/kg for white rats. The approximate oral LD-50 is 1.4 mg/kg for white rats. It is readily acceptable to rats in 0.5% mixture with food, producing convulsions and death in 5–12 minutes in most animals. It is of potential interest in the treatment of muscular diseases such as myasthenia gravis because of its powerful anticholinesterase activity and is being investigated pharmacologically with this in view.

The effect of 2,3-dimercaptopropanol upon the diuretic action of mersalyl. G. MARESH, JR. and A. FARAH (introduced by O. Kraye). *Dept of Pharmacology, Harvard Medical School*. Mersalyl diuresis was studied in unanesthetized rabbits since rats and mice were found unsatisfactory for the production of such a diuresis. Fifteen to eighteen hours before an experiment the rabbits were given by stomach tube 0.25 grams of ammonium chloride per kg, and 20 cc of normal saline per kg. Mersalyl, 10 mg/kg, was given intravenously followed in 1–2 minutes by an intravenous injection of 2.3 dimercaptopropanol. Urine was collected every 30 minutes for 5 hours. The total chloride excretion for the 5 hour period was determined by the method of van Slyke and Sendroy.<sup>1</sup> It could be shown that about 2 mg/kg of 2.3 dimercaptopropanol completely inhibited the increased water output produced by 10 mg of mersalyl per kg. The increased excretion of chloride induced by mersalyl was also prevented by this dose of 2.3 dimercaptopropanol and the chloride output stayed roughly proportional to the total output of urine. Furthermore, 2,3 dimer-

captopropanol could abruptly stop a diuresis produced by mersalyl. Cysteine was 10–20 times less effective in inhibiting a diuresis by mersalyl. The diuresis produced by 5% sodium chloride solution and by aminophylline was not appreciably altered by 2,3-dimercaptopropanol.

The differential effects on synaptic transmission and nerve conduction of di-isopropyl fluorophosphate (DFP) and atropine. AMEDEO S. MARRAZZI and NORMAN E. JARVIK (by invitation). *Wayne Univ College of Medicine*. Cholinergic phenomena are characterized by sensitivity to anticholinesterases and to atropine. The response to drugs of these types can, therefore, throw light on the nature of certain neural mechanisms.

The inferior mesenteric sympathetic ganglion of the cat, because of the fact that some preganglionic fibers run through it to enter the hypogastric nerve without having been interrupted in the ganglion, is used, according to the technique described by Marrazzi, as a convenient preparation in which the action potentials in the postganglionic hypogastric nerve simultaneously indicate synaptic events in the ganglion and simple conduction in the fibers merely traversing it. During the delivery of fixed shocks to the inferior splanchnic (preganglionic) nerve the control level of response is recorded in the direct or non-synapsing fibers (B or D waves) and in the postsynaptic fibers (C waves) of the hypogastric nerve.

DFP increases the C without affecting the D waves. Atropine decreases the C, likewise without affecting the D waves. These and other records will be presented showing that synaptic transmission and axonal conduction through the inferior mesenteric ganglion of the cat can be differentiated by their response to drugs of this type and the argument is developed that the mechanisms of the neural processes involved must, therefore, be different. The well known greater resistance of axons to agents capable of modifying synaptic functions thus extends to drugs acting on cholinergic systems and suggests the further use of such drugs as anlytic agents. [Aided by a grant from the Smith, Kline & French Laboratories.]

Synthetic curare compounds. I. Biochemical aspects of quaternary ammonium iodides derived from cinchona alkaloids. DAVID FIELDING MARSH. *Dept of Pharmacology, West Virginia Univ School of Medicine, Morgantown, W. Va.* The curariform activity of the quaternary ammonium salts of quinine has been well established. In this study, quinidine methiodide (N-methyl quinidinium iodide), quinidine ethiodide, cinchonine methiodide, cinchonine ethiodide, cinchonidine methiodide, cinchonidine ethiodide were compared with quinine methiodide and quinine ethiodide.

The cat gastrocnemius preparation, with the

<sup>1</sup> The determination of chlorides in blood and tissues. van Slyke and Sendroy. *J Biol Chem* 58: 523, 1924.

peripheral end of the cut sciatic nerve stimulated with a relaxation oscillator, is completely paralyzed by the systemic administration of these agents at 1-3 mg/kg, with the quinidine compounds being most potent, then cinchonidine, quinine and cinchonine least. Equivalent doses of curare extracts (Intocostin) are roughly four times as potent. Like curare, these agents produce an accompanying, transient fall in blood pressure that is incompletely antagonizable by atropine, and is not related to oxygenation of the animal.

The relative activity was determined by the head drop assay in rabbits and compared with the lethal intravenous dose in rabbits, as well as the paralytic and lethal intraperitoneal doses in rats. Although the quinidine and cinchonidine compounds are most active and most toxic, the quinine compounds produce better lissive action with less fasciculation and convulsive movement while the cinchonine compounds are least active. The relative safety margin of these compounds is quite small.

The effects of benzyl-imidazoline (priscol) in partially sympathectomized dogs F. A. MARZONI (by invitation), M. J. REARDON (by invitation) and JAMES P. HENDRIX, *Depts. of Surgery and Medicine, Duke Univ. School of Medicine, Durham, N. C.* It has been shown that priscol reverses epinephrine pressor effect and in larger doses blocks the pressor effect of splachnic stimulation (Chess and Yonkman, *Fed. Proc.* 4: 114, 1945). We have studied the effect of priscol on blood pressure, certain vascular reflexes and "peripheral resistance" in dogs under chloralose anesthesia, subjected to unilateral lumbar sympathectomy. Blood pressure was recorded by a mercury manometer from the femoral artery. An estimate of peripheral resistance in the legs was obtained, using similar manometers, from the distal ends of severed femoral arteries.

We have shown that priscol in adequate dosage prevents the rise in blood pressure resulting from bilateral carotid artery occlusion and faradization of the central end of the severed vagus nerve; we also have confirmed the adrenolytic action of priscol. After priscol "peripheral resistance" in the normal leg declined to the level of the sympathectomized leg and was nearly parallel in the two.

Results follow. Bilateral carotid occlusion marked pressor effect, "peripheral resistance" increased in normal leg, slower, passive response in sympathectomized leg. After priscol, no pressor effect, little or no change in "peripheral resistance."

Epinephrine 0.3 mg i.v. marked pressor effect, "peripheral resistance" increase more immediate and marked in sympathectomized leg. After priscol, depressor or no response, passive response in

resistance sympathectomized leg, little or no response normal leg.

Central vagus stimulation. Results comparable to those of carotid occlusion.

Summary of effects in relation to dosage. Priscol mg/kg i.v.

1-3 Temporary pressor effect

3-6 Adrenolysis, diminution of pressor reflexes

6-15 Depressor effect, adrenalin reversal, abolition of pressor reflexes

[Aided by a grant from Ciba Pharmaceutical Products, Inc.]

Effects of feeding uranium nitrate in the diets of breeding white rats. ELLIOTT A. MAYNARD, CHALLISE RANDALL and HAROLD C. HODGE (introduced by H. B. Haag). *Division of Pharmacology and Toxicology, Dept. of Radiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* A question which arose early in the toxicological study of Uranium compounds under the Manhattan program was the effect of ingestion of Uranium on ovaries and testes. An experiment was set up in which pairs of control rats were fed stock diet and pairs of experimental rats were fed a diet containing 2.0% U nitrate. The rats were allowed to mate, the females were separated from the males late in pregnancy. The litters were removed on the day of birth and the females were returned to the males. The number of litters and the number of young per litter were recorded, growth records were kept.

After 195 days about 1 as many litters and pups had been born to the experimental rats as to the controls. At the end of 195 days the rats which had been receiving U nitrate in the diet were placed on the same stock diet as the controls for the balance of the year.

During 5 months on the control diet the females which failed to have litters while ingesting U nitrate continued not to have litters. A slight increase in birth rate occurred in the experimental females which bore litters previously. At the end of the experiment the experimental rats had almost attained the weights of the controls.

From the 4th to the 7th months of the experiment daily vaginal smears were made to observe the regularity of the oestrus cycle of all females in relation to their regularity of mating. Marked irregularity of oestrus cycles accompanied by irregularity of mating occurred in the experimental rats, no irregularity of oestrus cycles occurred in the controls.

On the toxicity of curare in animals maintained with artificial respiration. E. L. McCawley and J. BELFORD\* (by invitation). *Dept. of*

\*Supported by Fluid Research Funds Yale University School of Medicine

\*National Institute of Health Research Fellow in Pharmacology Yale University

*Pharmacology and Toxicology, Yale Univ School of Medicine, New Haven, Conn* Curare is finding increasing clinical usage in providing muscular relaxation. With the use of artificial respiration and endotracheal catheters problems of toxicity have been minimized. Since this permits the usage of larger doses of curare it is necessary to investigate the possibilities of other deleterious side effects e.g., central nervous system and heart.

Data were recorded using an ink writing oscillograph adapted for measuring EEG, EKG and blood pressure. Cats (2 kg) were lightly anesthetized with pentobarbital sodium, 30 mg/kg, and provided with artificial respiration (20/min). Curare (Intocostin and d-tubocurarine chloride supplied through the courtesy of E. R. Squibb and Sons) was injected slowly in divided doses using a saphenous vein.

Intocostin, 3-5 units/kg, is a "lissive" dose and produces little else other than spasms in an unanesthetized animal. At 10 units/kg there is a slowing of the EEG, high amplitude slow waves 7-9/sec predominate and low voltage fast activity is suppressed. If this dose be repeated at 10 minute intervals for five doses there is no appreciable cumulation and there are no additional effects when fifty units per kg per dose was given the EEG was depressed for periods of 12-26 seconds. At 100 units/kg, after two such doses, all EEG activity disappears. The EEG did not return in 1-4 hour observation periods.

d-Tubocurarine eliminated the EEG following 330 units/kg (45 mg/kg) but should not be compared with the above reported Intocostin experiment as the time intervals of administration differed.

On the EKG the QRS segment and T waves were depressed above 100 units/kg of both curare preparations. There was in addition a slight fall in blood pressure and increase in pulse rate. However, a total of 860 units/kg of Intocostin failed to stop the heart when given over an 80 minute period.

A method for simultaneous recording of pharmacological and physiological data<sup>1</sup> E. L. McCawley, A. Mauro<sup>2</sup> (by invitation) and R. G. Grenell *Labys of Pharmacology and Neuroanatomy, Yale Univ School of Medicine, New Haven, Connecticut*. In determining cause and effect of physiological events, time relationships are of primary importance. At the present time, the effects of drugs on respiration and blood pressure are measured, using smoked drum kymographs, the electrocardiograph, electroencephalograph, and nerve or muscle action potentials are

measured with separate instruments, and frequently on another animal. When the mechanical and electrical recording are combined in the same system, it becomes unnecessary to duplicate an experiment to obtain the additional data. Moreover, since the recordings are simultaneous, any interrelation of one functional event with another can easily be correlated.

Ink writing oscillographs of the type used in electroencephalography have been adapted so as to record, on a single sheet of paper, as many as eight simultaneous phenomena. These instruments have the advantage of being simple to operate and maintain, and also minimize inertia effects and mechanical distortions.

The electroencephalogram and electrocardiogram are recorded directly by means of the usual leads to the preamplifiers. Muscular movements can be recorded easily on the oscillograph as a variety of methods exist for converting such motion into changes of electrical current, e.g., Piezo-crystal.

Blood pressure, respiration (frequency and volume), pH and temperature are recorded on the oscillograph by use of Wheatstone bridges in conjunction with a carrier current amplifier system.

The purification of histamine for bioassay. FLOYD C. McINTIRE, L. W. ROTH, and JOSEPH L. SHAW (introduced by H. B. Haag) *Biochemistry and Pharmacology Depts., Abbott Labs., North Chicago, Illinois*. Procedures by which histamine may be purified for bioassay generally involve either too many manipulations or too elaborate equipment for routine application to numerous samples. The authors have developed a purification procedure for histamine which is well suited for use with a large number of samples. As many as 50 samples of rabbit plasma have been carried through this procedure in 3 to 4 hours. This procedure probably is also more selective for histamine than most other methods. The steps are briefly as follows:

Anhydrous sodium sulphate and trisodium phosphate are added to an aqueous solution of histamine to give a M/1 solution of trisodium phosphate which is nearly saturated with sodium sulphate. This solution is shaken thoroughly with an equal volume of n-butanol. The butanol phase is transferred to a tube where it is filtered through a cation exchange material (cotton acid succinate) which takes up the histamine. The histamine is removed from the cation exchanger by washing with dilute hydrochloric acid. The strength of the acid is so chosen that when it is neutralized with sodium hydroxide a physiological salt solution is obtained which can be assayed directly. Histamine recoveries through this procedure are 95 to 100 per cent of the theoretical value.

<sup>1</sup> Aided by a grant from The Fluid Research Funds, Yale University School for Medicine.

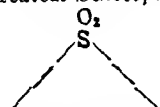
<sup>2</sup> U. S. Public Health Service Research Fellow in Biophysics, Yale University.

Pharmacological antagonism between stereoisomers of hexachlorocyclohexane B P Mc NAMARA (introduced by Stephen Krop) *Pharmacology Section, Medical Division, Edgewood Arsenal, Maryland* There are four known spatial isomers of hexachlorocyclohexane The intravenous administration of the gamma isomer ("gammexane") produced convulsions and other clinical manifestations of central stimulation in normal rabbits and dogs The delta isomer produced symptoms of central depression in these species Prophylactic treatment with the delta compound reduced the mortality produced by the gamma isomer In curarized dogs, "gammexane" elicited a "grand mal" type of electroencephalogram with concomitant rise of blood pressure and bradycardia Prophylaxis with the delta isomer prevented these effects In dogs anesthetized with pentobarbital, however, "gammexane" did not evoke "convulsive" type electroencephalograms Moreover, it produced a profound fall of blood pressure with bradycardia in the anesthetized dog

Local and systemic effects of 2-methyl 2, 4 pentanediol (hexylene glycol) W A McOMIE<sup>1</sup> (introduced by Hamilton H Anderson) *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San Francisco* Woodward, et al (Fed Proc 4 142, 1945) have reported previously on the toxicity of this compound Our findings were similar, e g the acute intragastric LD<sub>50</sub> for mice was found to be 3.8 ml/kg In rabbits no deaths occurred after 24 hours exposure to doses ranging from 3.9-9.4 ml/kg when applied to the skin by the cuff method of Draze, et al (J Pharmacol 82 377, 1944) Local effects consisted of slight erythema and in one of the five animals a slight edema occurred Five rabbits were then exposed 15 times in a period of 20 days to 10 ml (approximately 3.0 ml/kg) applied to the shaved dorsal surface No other effects were noticed Upon sacrifice no pathologic changes were observed The action of this glycol on the rabbit's eye resembled that of 95% ethanol rather than propylene glycol The acute systemic effects were attributed to its hypnotic action In mice, the hypnotic dose for 50% of the animals was about 3.5 ml/kg, intragastrically and about 2.5 ml/kg, intraperitoneally The margin of safety would appear to be small Pulmonary congestion and hemorrhage were found in mice after either intragastric or intraperitoneal administration possibly indicating the presence of a volatile, irritant metabolite

Analeptic properties of 2,4-dimethyl sulfolane W A McOMIE (by invitation), R W PICKERING

(by invitation) and HAMILTON H ANDERSON<sup>1</sup> *Division of Pharmacology and Experimental Therapeutics, Univ of California Medical School, San*



Francisco A new agent (CH<sub>3</sub>CHCH CHCH<sub>3</sub>-CH<sub>3</sub>, (DMS) was investigated for analeptic activity (method of Goodwin and Marshall, J Pharmacol 84 12, 1945) and barbiturate antidoting effect (method of Chakravarti, Ibid 67 153, 1939) in comparison with metrazol (M) and picrotoxin (P) In the table results in mice are summarized

Dose level <sup>a</sup> LD <sub>50</sub>	Analeptic ratio			Mortality ratio (after Na pentobarbital (PBL))	
	DMS	M	P	DMS	M
0.25				13/20	9/20
0.5	0.75	0.69 <sup>d</sup>	0.59 <sup>d</sup>	5/20	8/20
1.0	0.63	0.47	0.54	3/30	1/30
2.0	0.53	0.36	0.59	1/20	1/20
4.0	0.36		0.40	3/20 <sup>c</sup>	14/20 <sup>c</sup>

<sup>a</sup> LD<sub>50</sub> (I P) in mice was found to be 31 mg/kg for DMS and 92 mg/kg for metrazol from data of Chakravarti 4.5 mg/kg for picrotoxin

<sup>b</sup> Without treatment 22/23 mice died after PBL (140 mg/kg I P)

<sup>c</sup> Deaths were due to convulsive effects of analeptic

<sup>d</sup> Data of Goodwin and Marshall

DMS decreased sleeping time of mice after PBL I V, similar to M and P Since the molecular weights of DMS (148) and M (138) are similar, they have a similar molar order of activity DMS, equally effective as M against PBL, exhibited greater safety at higher doses

DMS promptly increased respiration in rats and rabbits depressed with PBL Oxygen consumption of rats depressed to 60% of normal (by 40 mg/kg, PBL, I P) returned to normal after 40 and 80 mg/kg of DMS, I P Rabbits depressed with PBL, then given 25 mg/kg DMS, I V showed an immediate rise in rate and amplitude of respiration Minute volume was more than doubled within 10 minutes after 25 mg/kg of DMS, I V, while M at the same dose caused less than 50% increase Duration of action was similar

A protein-free fraction from desiccated thyroid substance of physiologic action ARTHUR L MEYER<sup>2</sup> and JEAN P McEWEN<sup>2</sup> (introduced by Arthur A Hellbaum) *From The Maltine Therapeutic Foundation, Brooklyn, N Y* An extract has been prepared from commercial desiccated thy-

<sup>1</sup> Aided by a grant from the Shell Development Company, Emeryville, California

<sup>2</sup> Dr Warren L Bostick, Division of Pathology, University of California Medical School, examined sections of tissues

<sup>1</sup> Supported in part by a grant from the Shell Development Company, Emeryville, California, who supplied the 2,4-dimethyl sulfolane

Present address of both authors: Res Labs, Fellows Medical Wfg Co Inc, New York 14

roid that is soluble in water and alcohol, insoluble in ether. It is an amorphous material containing up to 0.94% of iodine and at an average 5% of choline. In assays on the frog's rectus muscle the choline content, as found chemically, was confirmed. The substance does not contain acetylcholine. The physiological action, essentially of parasympathetic character, is 20 times higher than corresponds to the choline content and differs from that of choline qualitatively. The intestine is more evenly stimulated than by choline. It depresses the blood pressure in the dog, cat and rabbit in ether anesthesia. It produces a negative and later positive inotropic effect on the heart *in situ* as well as during perfusion by Langendorff's method without a lasting dromotropic effect. Respiration is temporarily retarded. The intestine *in situ* is stimulated by systemic application. It is stable against heating with acid and alkali and retains a large part of its potency after atropinization. This behavior differentiates it from histamine, adenosine compounds and Euler and Gaddum's factor P. Analogous extracts, prepared from other organs, contained approximately the same percentage of choline. Liver extract was less efficacious and contained adenosine compounds, splenic extract was characterized by a significant histamine content and testicular extract had only as much activity as corresponded to its choline content.

**The effects of thiosorbitol and of iodides on alphanaphthylthiourea toxicity in rats** BERTRAM J. MEYER and LEONARD KARFL (introduced by Stephen Krop) *Toxicology Section, Medical Division, Edgewood Arsenal, Md.* Of 19 compounds tested only thiosorbitol (Huvey and Tatum, '47) and potassium iodide (Bycium, '46) were successful in counteracting the effects of ANTU. Negative results were obtained with antihistamine drugs (benadryl, pyribenzamine), vasomotor drugs (ephedrine, eoramine), aliphatic and aromatic amino acids (glycine, paraaminobenzoic acid, nicotinic acid), several sulphydryl and labile sulfur compounds (cysteine, BAL, sodium thiosulfate), a hexanhexol (sorbitol), aldehydes (dextrose, n-heptaldehyde), a melamin precursor (tyrosine), a prophylactic against phosgene pulmonary edema (hexamethylenetetramine) and therapeutically administered organic iodides (amyl iodide, iodoacetic acid).

Prophylactic and therapeutic tests were conducted on albino Wistar rats divided into groups of ten. Injections of ANTU (or in a few instances, phenylthiourea) were limited to not more than 2 intraperitoneal LD<sub>50</sub>'s, equivalent to ca. 90-95 per cent mortality. Potassium iodide given in the drinking water (176 mg/ml) for 44 hours prior to the injection of 2 LD<sub>50</sub>'s decreased the number of deaths to 1/10. A total of 250 mg of potassium iodide per kg administered subcutaneously in 6

doses over a three day period resulted in a 4/10 mortality. Lower doses given either prophylactically or therapeutically by different routes failed to protect. Thiosorbitol, 1.5 grams/kg, given either intraperitoneally or intramuscularly simultaneously with ANTU reduced the mortality of 1 LD<sub>50</sub> to about 10 per cent and of 2 LD<sub>50</sub>'s to approximately 40 per cent. No decrease in mortality was obtained when 2.5 LD<sub>50</sub>'s of ANTU were used. However, animals receiving thiosorbitol exhibited a definite delay in time of death compared to the controls.

**Site and mode of action of several cholinesterase inhibitors** DOROTHEA STARBUCK MILLER and BENSON GINSBURG (introduced by E. M. K. Geiling) *Toxicity Lab. and College, Univ. of Chicago*. In order to test the hypothesis that cholinesterase inhibitors owe their physiological activity to the accumulation of free acetylcholine centrally and/or peripherally, determinations of free acetylcholine were made in brain and submaxillary gland of mice and rats following injection of prostigmine, physostigmine, a prostigmine analogue, and di-isopropyl fluorophosphate. Prostigmine, physostigmine, and the prostigmine analogue produce an appreciable increase in free acetylcholine at end organs (submaxillary gland) but not in brain, while DFP produces a threefold increase in brain acetylcholine but has only a slight end-organ effect. Survivors and non-survivors of LD-50 doses of the prostigmine analogue or of DFP show no significant difference in free acetylcholine content of either brain or submaxillary gland. The amount of acetylcholine liberated at the principle site of action of a cholinergic drug does not seem to be the factor primarily responsible for its physiological activity.

Dogs treated with the prostigmine analogue (Ginsburg and Elder) showed abnormally high plasma glucose and inorganic phosphorus levels. Pretreatment with insulin gave protection against otherwise lethal (LD-100) doses of the prostigmine analogue. Insulin protection was obtained in mice, was less effective in rats, and was ineffective in guinea pigs. Insulin treatment did not affect the acetylcholine level unless shock was produced. These results suggest that the ability of parts of the nervous system to utilize glucose may be impaired by cholinergic drugs and that this effect upon glucose metabolism may be important to an understanding of their mode of action.

**Relative importance of digitalis and mercurial diuretics in the treatment of advanced heart failure** WALTER MODELL, MORRIS PLATTENBERG (by invitation), and DONALD A. CLARKE (by invitation) *Dept. of Pharmacology of Cornell Univ. Medical College, and Cardiac Services of Beth Israel Hospital and Hospital for Joint Diseases, New York*. The relative importance of digitalis and

mercurial diuretics was explored in 47 ambulatory cardiac patients with chronic advanced heart failure who required mercurial diuretics to maintain reasonable comfort. In 30 there was a normal sinus rhythm, in 17 auricular fibrillation.

The study was carried through 2 consecutive periods. An 8 week control period during which the patient received digitalis and mercurial diuretics, followed by an 8 week period during which the mercurial was continued but digitalis was withdrawn. Objective signs of failure (weight, ventricular rate, liver size, ankle edema), and the patient's subjective condition were noted at weekly intervals.

In 78 per cent continuation of the mercurial in the absence of digitalis for the 8 week period did not disturb the control of failure, while in the remaining patients, there was a marked progression of failure. There was auricular fibrillation in 90 per cent of the latter group, and in only 20 per cent of the former. On withdrawing digitalis, acceleration of the ventricular rate occurred in all patients with auricular fibrillation.

Factors other than the aberrant cardiac rhythm, age, sex, etiology, anatomical lesion, appeared to play no role in determining the dependence on digitalis.

It is suggested that, in patients with chronic advanced failure who require mercurial diuretics, the mercurial is of greater importance in the control of the heart failure than digitalis, but that in such cases with auricular fibrillation, digitalis may continue to serve a useful purpose which is not as apparent in those with a normal rhythm.

The action of tetraethylammonium on receptor mechanisms. GORDON K. MOE, RICHARD H. LYONS (by invitation), SIBBELY W. HOOBLER (by invitation), and ROSALIE NELIGH (by invitation). *Depts. of Pharmacology and Internal Medicine, Univ. of Michigan.* In certain patients with arteriosclerotic disease of the extremities tetraethylammonium (TEA) has been shown to relieve pain without causing an increase of skin temperature or of hand blood flow. These observations suggest interruption of pain pathways, either centrally or at the sensory endings. Except with excessive doses no failure of sensory perception occurs in normal subjects. TEA does not prevent the pain induced by repeated contraction of the muscles of an arm in which the circulation has been interrupted by application of a tourniquet. The mechanism of pain relief in certain vascular disorders is therefore obscure.

The only receptor thus far studied which is blocked by TEA is the carotid body mechanism. The hyperpneic response to injection of large doses of acetylcholine in the atropinized animal, and the hyperpnea induced by nicotine and other similar compounds can be blocked by continuous infusion of TEA. The inhibition ap-

pears to be competitive, for larger doses of the stimulant compounds will again cause respiratory stimulation, which can in turn be blocked out by increasing the rate of infusion of TEA.

If this blockade were central rather than peripheral, the reflex response to cyanide should also be abolished, but this is not the case, TEA does not diminish the respiratory stimulation produced by cyanide. Interruption by TEA of the response to acetylcholine of this unique receptor organ may be based upon the embryological relationship between the carotid glomus and the sympathetic ganglia. [Aided by a grant from the Life Insurance Medical Research Fund.]

Reproductive tract modification in the female opossum during and following exposure to light. CHARLES F. MORGAN (introduced by T. Koppman). *Dept. of Pharmacology and Materia Medica, Georgetown Univ., School of Medicine.* Daily increasing increments of light from incandescent lamps caused a stimulation of the atrophic reproductive tract of the adult female opossum during the anestrus nonbreeding season. Weekly laparotomies were made, measurements obtained showed that exposure to light was without stimulating effects until total daily intensity reached a threshold, after which weight and size responses were noticeable. Lights stimulated reproductive tissues in control animals with eyes removed and those with optic nerves cut. Histological preparations revealed in abundance almost cystic ovarian follicles in light treated animals, while anestrus controls had only a few small follicles. Uterine endometrium showed the greatest stimulation. Cornification of the epithelial lining of the vaginal sinus occurred with estrus type "vaginal" smear. The stimulation varied with light intensity. In cages receiving light intensities of 15, 10, and 6.5 foot candles at the front, middle and back, respectively, the average increase of ovarian weight was 2.1 times and of uterine diameters 1.5 times those of the normal anestrus opossum. In cages with increased light intensities of 25-, 15- and 12 foot candles at the front, middle and back, an average ovarian weight increase of 3.3 times and average uterine diameter increase of 2.8 times those recorded for the anestrus opossum resulted. All stimulation ceased and organs under observation resumed appearance of atrophic anestrus reproductive system when daily exposure to light was reduced below threshold values, or when the animals were returned to normal daylight intensities of December.

The effect of tetraethylammonium bromide on morphine hyperglycemia in dogs. JAMES L. MORRISON. *Dept. of Pharmacology, Emory Univ., Georgia.* The blood sugar of normal fasting dogs rises rapidly following subcutaneous injection of 10 mg./kg. of morphine sulfate—it times becoming two or three times as high as the normal level in



following injection. On the basis of this relationship a quantitative assay has been devised for the determination of pyrogens in water and biological materials. For this assay a "pyrogen unit" has been adopted and defined as the quantity of pyrogen per kg of body weight causing an average rise of 1.0°C in rectal temperature. A standard curve conforming to this definition has been established for evaluating assay results. The biometrical basis for the standard curve and the reproducibility of results in routine assays will be described.

Sulfathiazole clearance as a measure of glomerular filtration rate. S. ANDERSON PEOPLES, DON W. CHAPMAN (by invitation), and H. F. ARNOLD (by invitation). *Dept. of Physiology and Pharmacology, and Dept. of Medicine, Baylor Univ. College of Medicine, Houston, Texas*. Simultaneous clearances of sulfathiazole and creatinine were determined in ten dogs. When corrected for the fraction of sulfathiazole bound by the serum albumin, the ratio of the clearances was  $1.00 \pm 10\%$ . The free/total ratio was determined by ultrafiltration and can be calculated from the formula

$$\text{Free/total} = \frac{1}{K \times \text{Albumin} + 1}$$

where  $K = 0.32$ . Low clearances were obtained when the urine pH fell below 7.2 and high values when it was above 7.7.

Simultaneous clearances of sulfathiazole and inulin were determined on 20 human subjects with normal and diseased kidneys. The free sulfathiazole was calculated from the above formula except that  $K = 0.45$ . The ratio of the two clearances was  $1.0 \pm 15\%$  both in the controls and patients with renal disease. The pH of the urine is not as important a factor as it is in the dog in that good agreement was obtained between the pH range 6.2-7.8.

The sulfathiazole clearance gives an accurate measure of the glomerular filtration rate in both the dog and man. It is of particular usefulness in man since the sulfathiazole is given orally, and necessary determinations are easily carried out.

Investigation of 1'-ethyl-3,6-dimethyl-2-phenyl-4-pyrimido-2'-cyanine chloride (C M R Center No. 863) for possible therapeutic utility in human filariasis. LAWRENCE PLIERS, AEMI HIGASHI (by invitation), and ARNOLD D. WILCH. *Dept. of Pharmacology, School of Medicine, Western Reserve Univ., Cleveland, Ohio*. This compound, in addition to possessing marked antifilarial activity against *L. carinii*, produced less vasodpression and less local tissue damage than other cyanines studied. Local injury following subcutaneous injection was sufficient, however, to prohibit administration by this route; further, much of the drug was retained at the injection site. Massive oral doses produced only occasional cures.

Since the drug was as effective when adminis-

tered intraperitoneally once daily as when given at 8-hour intervals, intravenous therapeutic experiments were devised. In these, cotton rats infected with *L. carinii* were employed, experimental variables were the magnitude of individual or total doses, and the interval between individual dosages. Cures resulted in practically all cases after the intravenous administration of 6 doses, each of 10 mg of #863 per kg, with dosage intervals of 1, 3 or even 7 days.

The maximally tolerated single intravenous dose on all schedules appeared to be 10 mg/kg, fatalities consistently occurred at higher levels of dosage.

Extensive toxicological studies in dogs and in monkeys have been based on similar schedules of intravenous dosage; these disclosed a mild and reversible renal damage at high dose levels as the only chronic toxic manifestation. Through facilities afforded us by the School of Tropical Medicine, San Juan, Puerto Rico, preliminary therapeutic trials of this compound have been initiated in human subjects infested with *Wuchereria bancrofti*. Data on these therapeutic trials, derived from changes in the number of circulating microfilariae, are now being collected.

The chronic toxicity of 1'-ethyl-3,6-dimethyl-2-phenyl-4-pyrimido-2'-cyanine chloride (C M R Center No. 863) for dogs and monkeys. LAWRENCE PLIERS, WILLIAM B. WARFMAN, ALLEN MOORE (by invitation), AEMI HIGASHI (by invitation), and ERNST BUEDELING. *Dept. of Pharmacology, School of Medicine, Western Reserve Univ., Cleveland, Ohio, and Dept. of Pathology, School of Medicine, Northwestern Univ., Chicago, Illinois*. This compound was administered intravenously to dogs and monkeys, by syringe or venoclysis, in doses of 5 to 10 mg/kg at intervals of 2, 3 or 7 days for 6 to 10 weeks. Blood counts, and the concentration of hemoglobin and of plasma proteins, remained at normal levels. Liver function, as indicated by plasma protein, and bilirubin values, bromsulfalein and thymol-turbidity tests, remained normal and glucose tolerance curves were unchanged. Hematologic studies in growing albino rats confirmed the findings in dogs and monkeys.

Gross and microscopic study of organs removed at autopsy showed no pathologic changes except in the kidneys. The convoluted tubules (in most cases, the proximal tubules) showed some cloudy swelling, with increased staining properties. The glomeruli were unaltered, cellular infiltration was practically absent, and no nuclear changes suggestive of necrosis occurred. Only in a few cases, at high dose levels, was there a concomitant decrease in renal function, as indicated by uremia and by decreased creatinine and p-aminohippuric clearances. In these cases the uremia was readily reversible, if therapy was discontinued. Additional therapy led to permanent uremia with little in-

tensification of histologic changes. The relative role played by the vasodepressor effect of this compound and its presence *per se* in high concentrations in renal tubular cells remains to be elucidated.

Since no pathologic changes followed the use of this drug, as described, except reversible alterations in the kidney, the drug was given cautious clinical trial in man. No evidence of systemic toxicity was seen.

**Time relationships in the reversal by BAL of the chemotherapeutic effect of mapharsen.** CARL C. PFEIFFER, ELIZABETH H. JENNEY (by invitation), and CHARLES A. ROSS (by invitation). *Dept. of Pharmacology, Univ. of Illinois College of Medicine, Chicago 12.* When rats heavily infected with *T. equiperdum* were treated with an intravenous dose of 5 mg/kg of Mapharsen, the trypanosomes, as determined by microscopic inspection, disappeared from the peripheral blood within 15 to 45 minutes. When BAL (75 mg/kg) was given intramuscularly in oil within 5 minutes after the intravenous dose of Mapharsen, the trypanosomes (per cu. mm) did not decrease, thus indicating a prompt and complete reversal of the chemotherapeutic effect. If the BAL injection was delayed a reversal of the chemotherapeutic effect was obtained up to three hours after the disappearance of the trypanosomes from the peripheral blood. Thus ten out of thirteen rats relapsed when BAL 75 mg/kg was given three hours after "apparent cure," as shown by the disappearance of motile forms from the blood stream. All of the control rats were cured with 5 mg/kg of Mapharsen. The data are interpreted as indicating 1) a latent focus of trypanosomiasis in some organ of the rat or a quiescent capillary blood flow effect, 2) a pleomorphic and more resistant form of the trypanosome, or 3) the failure of microscopic examination to reveal occasional non motile forms of the trypanosome which would eventually be phagocytized. Transplants of the organs of Mapharsen treated rats to BAL treated recipients indicate that the later hypothesis is the most probable.

**Antidiuretic response in dogs following intracarotid injection of hypertonic sodium chloride solution.** CALVIN PLUMHOF, J. VICTOR STEVENSON and JAMES L. P. TOMAN. *Depts. of Pharmacology and Physiology, Univ. of Utah School of Medicine, Salt Lake City, Utah.* Preliminary studies were undertaken to determine whether the hypothalamic pituitary system could be activated directly. Adult female dogs anesthetized with pentobarbital were hydrated *in vivo* with sufficient hypotonic 0.3% NaCl solution (100 cc/kg) to produce a control diuresis. Glomerular filtration rates (creatinine clearances) were followed and urine volumes determined at 15 minute intervals. Hypertonic (25%) NaCl solution (2.5 cc/kg/min) was in-

jected over a 2 minute period directly into the common carotid artery. Osmotic balance was maintained by simultaneous intravenous (femoral) infusion of 0.3% NaCl solution.

Intracarotid hypertonic solution reduced urine flow to 25% to 35% of the control. This reduction was accompanied by increased percentage reabsorption, since filtration rates were not appreciably changed. Post pituitary substance (4 units/kg) produced an equivalent reduction in urine flow (Anesthetized animals are quite refractory to exogenous post-pituitary extract). Urine collected from dogs receiving intracarotid hypertonic NaCl solution produced marked antidiuresis when injected (2 cc/kg) into an unanesthetized bioassay dog, without changing filtration rate; control urine exhibited no antidiuretic action.

These results confirm for anesthetized animals the observation of Verney (Lancet 251:781, 1946) that antidiuresis follows intracarotid injection of hypertonic solutions in unanesthetized dogs. In addition, the present experiments indicate that the antidiuresis is not attributable to systemic effects of hypertonic solutions, that it is accomplished by increased tubular reabsorption, and that it is associated with the appearance of an antidiuretic substance in the urine. The results present additional evidence for direct activation of the hypothalamic pituitary system by a hypertonic environment.

**Comparative measurements of the antihistamine effects.** H. J. PRATT (by invitation), and R. BEUTNER. *Dept. of Pharmacology, Hahnemann Medical College.* Freshly excised strips of guinea pig ileum suspended in Tyrode solution were constricted by the addition of 10 gamma of histamine to the bath (containing 100 cc at 38°C). The muscle lever was weighted in such a manner that the height of the excursion was 40-60 mm. Varying amounts of the drugs, listed in the following table, were then added to the bath and precisely one minute later the same dose of histamine was repeated. We determined the amount of drug which caused at least 50% reduction in the ileal spasm due to histamine. The data demonstrate the superiority of pyribenzamine, local anesthetics have only a feeble anti histamine effect.

Compound	Dose (mg per 100 cc)
Diethylamino-ethyl p-aminobenzoate HCl (Procaine)	50.000
Monobutyl amino ethyl p- amino benzoate HCl (Monocaine)	50.000
Methyl heptyl amino 2,2 dimethyl ethyl p-aminobenzoate HCl (Octocaine)	0.2500
Butyl- $\alpha$ -cyanine acid di-ethyl ethylene diamine HCl (Nupercaine)	0.1000
B dimethyl amino ethyl Benzhydryl ether HCl (Benadryl)	0.0025
Benzyl pyridyl diethyl ethylenediamine HCl (Pyribenzamine)	0.0005

The effect of neostigmine (prostigmine) on the actions of tetraethylammonium (etamon) in dogs and man M J REARDON (by invitation), F A MARZONI (by invitation), and JAMES P HENDRIX *Depts of Surgery and Medicine, Duke Univ School of Medicine, Durham, N C* Acheson and Moe (J Pharm & Exp Therap 87:220, 1946) and others have shown that the actions of etamon on the autonomic nervous system are due to block of efferent pathways in autonomic ganglia. Because of the known effects of prostigmine on ganglionic transmission we tried the effects of this drug during the course of experiments with etamon in dogs. Etamon produced typical effects of block of pressor reflexes, hypotension and loss of sensitivity of the cardiac vagus to faradization. After these effects were apparent 0.5-1.0 mg of prostigmine was given i.v. with rapid and dramatic relief of etamon effects, blood pressure rose, bilateral carotid occlusion again produced hypertension and the sensitivity of the cardiac vagus to faradization was restored.

Patients given etamon developed postural hypotension, abolition of response to carotid sinus pressure and expiratory breath holding, partial paralysis of accommodation and pupillary reflexes. Prostigmine 0.5-1.0 mg i.v. then caused rapid recovery of accommodation and pupillary reflexes, loss of postural hypotension, rise in B.P. from breath holding, and bradycardia with hypotension from carotid sinus pressure.

It is concluded that prostigmine antagonizes the effect of etamon on autonomic ganglia and that it is an effective antidote for the latter drug. This observation is of significance from the standpoint of the implications concerning the mode of action of etamon and also in the clinical use of the drug.

The effect of ureteral ligation, mercury bichloride, and phloridzin on the gluconeogenic function of the kidney of the eviscerated rat. ROGER M REINECKE, GUILFORD G RUDOLF, and MELVIN BRYSON (introduced by Leo T Samuels) *Dept of Biological Chemistry, Univ of Utah, Salt Lake City, Utah*. Ureteral ligation does not prevent the kidney from acting as a source of blood sugar. Mercury bichloride, however, apparently does eliminate this function. Furthermore, ureteral ligation does not interfere with this action of mercury. Phloridzination, on the other hand, does not prevent the gluconeogenic function of the kidney.

The ineffectiveness of ureteral ligation in preventing either renal gluconeogenesis or the toxic action of mercury suggests that this maneuver may not halt glomerular filtration in the rat. On the other hand, these findings taken with the observation that phloridzination is also ineffective in stopping the formation of sugar in the kidney, may indicate that this function is independent

from that by which glucose is resorbed from the glomerular filtrate [Supported by a grant from the John and Mary R Markle Foundation]

Renal excretion of the tetraethylammonium ion BARBARA R RENNICK (by invitation), GORDON K MOE, SIBLEY W HOOBLE (by invitation), ROSALIE NELIGH (by invitation), and RICHARD H LYONS (by invitation) *Depts of Pharmacology and Internal Medicine, Univ of Michigan*. The tetraethylammonium ion (TEA), like choline, forms a precipitate with Reinecke salt. This is the basis for a simple colorimetric estimation of TEA in urine.

In the dog and in man, nearly 100% of a parenterally administered dose of TEA can be recovered in the urine. In normal man, 50% of an intravenous dose is excreted in about 30 minutes, and 50% of an intramuscular dose in 300 minutes, only 5-15% of an oral dose can be recovered. Subjects with severe renal damage excrete the drug less rapidly.

In dogs 50% of an intramuscular dose appears in the urine in about three hours. Suspension of the drug in beeswax-propylene glycol mixture does not significantly delay excretion.

In several experiments TEA was infused into the left renal artery in anesthetized dogs. At infusion rates of 0.5 mg/min the extraction was 50-70%, indicating a tubular excretory mechanism. At higher infusion rates the extraction percentage diminished, approaching or falling below the values characteristic for substances excreted by glomerular filtration only. At low blood levels the drug is excreted more efficiently than at high levels, cumulation will occur in dogs when the drug is infused intravenously at a rate of 0.5 mg/kg/min [Aided by a grant from the Life Insurance Medical Research Fund].

Pharmacologic action of some quaternary ammonium derivatives of procaine. R K RICHARDS, L W ROTH (by invitation), and K KUETER (by invitation) *Dept of Pharmacology, Abbott Labs, North Chicago, Illinois*. The ethyl and methyl iodides of procaine, as well as the ethyl and methyl iodide of the dimethylamino analogue of procaine were prepared by Dr M B Moore. None of them are local anesthetic. They are more toxic than the tertiary compounds and fail to exhibit the marked convulsive action of procaine in guinea pigs. The ethiodide of procaine has been studied most intensively. In agreement with French workers (Hazard and Cortegiani, *Compt Rend Soc Biol*, 222, 921, 46), this compound was found to possess a marked pressor effect upon the blood pressure of the dog. This action was shown to be definitely of a nicotine like nature. In the cat, however, only the depressor phase of this action could be demonstrated. The paralyzing effect upon the superior cervical ganglion was of shorter

duration than that of nicotine Epinephrine continued to produce pressure responses in both species and to contract the nictitating membrane of the cat after this compound had acted upon the ganglia Preganglionic stimulation of the superior cervical ganglion became ineffective at this stage

Toxic effects of varying doses of kerosene administered by different routes J A RICHARDSON and H R PRATT-THOMAS (introduced by R P Walton) *Depts of Pharmacology and Pathology, Medical College of South Carolina, Charleston* In explaining the cause of death following accidental ingestion of kerosene emphasis has been given to the thesis that blood-borne kerosene absorbed from the gastro-intestinal tract acts to produce a characteristic type of pulmonary injury (Deichmann et al, *Ann Int Med* 21 803, 1944) The experiments reported here further demonstrate that typical lung injury can follow administration of kerosene by routes other than direct aspiration into the lungs as by intraperitoneal injection, intravenous injection, by direct injection into the stomach with cardia ligated and by introduction into Thierry fistula loops Consideration of dosage and degree of lung damage, however, favors the conception that aspiration is the most serious and usual feature of such poisoning as it occurs clinically (Waring, *Am J Med Sc*, 185 325, 1933, Nunn and Martin, *J A M A* 103 472, 1934) Intratracheal doses produced death or extensive congestion and consolidation in doses (per kgm) of 0.25 cc Comparable effects were obtained with intravenous doses of 0.5 cc Less marked effects followed intraperitoneal doses of 10 cc (rabbits), intragastric doses of 33 cc (dogs with cardia ligated), and stomach tube doses of 35 cc (rabbits) and 30 cc (dogs)

The response of patients with thiouracil-induced myxedema to desiccated thyroid DOUGLAS S RIGGS (introduced by Otto Krayer) *Laby of the Fairfield State Hospital, Newtown, Connecticut* Two euthyroid schizophrenic patients were treated with 0.6 to 0.9 grams of thiouracil per day Three to six months were required to produce any significant metabolic abnormalities Parallel decreases in basal metabolic rate and serum protein-bound iodine preceded the development of large soft vascular goiters Ultimate decrease of the serum protein bound iodine to zero suggested complete block of thyroid hormone synthesis If this block were assumed to exist from the beginning of thiouracil medication, there was a marked discrepancy between the time needed to attain myxedematous levels and the calculated daily output of hormone, assuming a normal initial store of preformed hormone

After a myxedematous state was clearly established, gradually increasing amounts of USP desiccated thyroid were administered while thiou-

racil was continued Approximately 200 milligrams of desiccated thyroid per day was required to restore the metabolic and biochemical status to normal, and to cause complete disappearance of the goiter The rate of response was similar to that of patients with spontaneous myxedema Larger amounts of thyroid up to 500 mgms per day caused disproportionately small further increases in the metabolic rate and serum protein-bound iodine, increases similar to those seen in euthyroid subjects taking large daily doses of thyroid On cessation of thyroid medication, the serum protein-bound iodine fell rapidly to subnormal levels, returning only slowly to normal

It was concluded that patients whose thyroids are completely blocked by thiouracil, exhibit tolerance to large amounts of desiccated thyroid similar to that seen in euthyroid subjects

Certain aspects of carbohydrate metabolism in normal animals and in animals poisoned with U-nitrate, U-chloride and alloxan EUGENE ROBERTS, CHARLES BISHOP (introduced by Raymond M Bieter) *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, The Univ of Rochester, Rochester, N Y* The purposes of these experiments were (a) to study and compare the effects of the inhalation of uranium salts and the injection of alloxan on glucose tolerance in rats and on the ability to form liver and muscle glycogen under standardized conditions and (b) to determine the effects in dogs of the inhalation of uranium nitrate on the levels of blood glucose, lactate and pyruvate at intervals following injection of glucose

There were no marked abnormalities in carbohydrate distribution before or after fasting in rats exposed to a dusty atmosphere of 19 mg/m<sup>3</sup> U-nitrate for 30 hours over a period of six days After the injection of glucose, however, the extra sugar could not be disposed of in a normal manner, and although the formation of liver glycogen was undisturbed, the glucose level remained irregularly high, reflecting a decreased ability of the animal to form muscle glycogen The difference could not be attributed to urinary excretion of the injected glucose Rats exposed for 12 hours to an atmosphere containing approximately 13 mg/m<sup>3</sup> of UCl<sub>4</sub> did not differ appreciably from normal rats in the fasted state, but lost the ability to remove normally injected glucose from the blood stream and to form and retain liver glycogen in the normal fashion The alterations in the carbohydrate metabolism in the poisoned rats were not comparable to those observed in diabetic rats which showed much higher glucose at all times and practically no ability to form liver glycogen The muscle glycogen values of the diabetic rats were also generally lower These findings are consistent with the failure to find any insulin producing abnormality in

**U-poisoned animals** The fluctuations in liver weight of all experimental animals at various time-intervals differed significantly from those established by the normal controls

The glucose tolerance curves of dogs undergoing an exposure to 19 mg /in<sup>2</sup> of U-nitrate were generally higher than normal. In dogs suffering from the acute effects of U-poisoning, the blood lactate and pyruvate curves in general failed to exhibit the characteristic rise at the one-quarter to one-half hour period after injection of glucose. Clinical recovery in the case of one dog was accompanied by a return to normal with respect to all criteria studied. The above findings are correlated with the biochemical disturbances resulting from the nephrotoxic action of uranium compounds.

**Studies on the toxicity of para-aminobenzoic acid in rats** EUGENE D. ROBIN (by invitation), CELIA WHITE TABOR (by invitation), and PAUL K. SMITH, *Dept. of Pharmacology, The George Washington Univ. School of Medicine, Washington, D. C.* The acute toxicity of para-aminobenzoic acid in rats was investigated by administering orally single doses of the drug suspended with acacia, or equivalent amounts of sodium para-aminobenzoate. A dose of ten grams per kilogram resulted in the death of approximately 90 per cent of the immature rats and about 45 per cent of the adult rats. When the soluble sodium salt was administered, hyperemia of the distal segment of the stomach was pronounced. Administration with acacia appears to diminish the degree of mucosal injection, without appreciable effect on the toxicity.

To determine the chronic toxicity of para-aminobenzoic acid, adult rats were maintained on a synthetic diet, with 4 per cent para-aminobenzoic acid added to the diet. During the two months they were observed, the only hematological change was a moderate leucocytosis in the experimental animals. These animals showed a moderate weight loss compared to the controls. When sacrificed, no gross pathology was observed.

A group of 10 day old rats was maintained on a diet to which 6 per cent para-aminobenzoic acid was added. After 28 days, no significant changes were observed in erythrocyte, leucocyte or platelet count. The experimental animals showed a 63 per cent mortality by the end of 1 month. [Supported by a grant from the Navy Department.]

**Effect of tetraethylammonium chloride on the urinary bladder of the cat** MAX A. ROOR (introduced by Otto Kravet), *Dept. of Pharmacology, Harvard Medical School*. Isometric records of partially filled bladders were made on cats which were either decerebrated or under chloralose anesthesia. Large single intravenous doses of tetraethylammonium chloride (1 to 3 mg /kg) were necessary to produce an effect on the bladder.

The normal rhythmic contractions of the intact bladder are abolished for 2 to 4 minutes. Return to normal rhythm is abrupt and no lasting change in tone occurs. In the acutely denervated bladder (pelvic and hypogastric nerves cut) tetraethylammonium chloride produces a slight rise in bladder tone and a decrease in the height of the contractions which last for 2 to 3 minutes. During stimulation of the pre-ganglionic pelvic nerves of the acutely decentralized bladder, tetraethylammonium chloride produces an effect identical with that produced in the intact bladder. In the acutely decentralized bladder tetraethylammonium chloride decreases the height of the abrupt contraction produced by either pre- or post-ganglionic stimulation of the hypogastric fibers. Tetraethylammonium chloride given during hypogastric stimulation (after the initial contraction) produces an effect identical with that produced in the decentralized unstimulated bladder.

**Some pharmacological properties of a new anti-histamine compound** L. W. ROTH (by invitation), R. K. RICHARDS and I. M. SHEPHERD (by invitation), *Dept. of Pharmacology, Abbott Labs., North Chicago, Illinois*. Pharmacological studies with—N( $\alpha$  pyridyl)-N( $\alpha$ -thenyl)-N', N'-dimethylethylenediamine hydrochloride (AH-42) have revealed the following.

AH-42 exhibits antihistaminic and anti-anaphylactic properties in a variety of tests. On the isolated guinea pig ileum strip, 0.002 micrograms/gram produced an inhibition of 75% or more to the subsequent contraction induced with 0.005 micrograms/gram of histamine (base). Repeated washing was necessary to eliminate all residual protection.

With rabbit intestine, the antispasmodic activity of AH-42 against barium chloride was approximately 50% that of papaverine, but only weakly effective against acetyl choline when compared to atropine.

In the anesthetized cat, depressor effects of small doses of histamine were markedly diminished by the previous intravenous administration of 10-20 micrograms of AH-42.

In guinea pigs, where the LD<sub>50</sub> of intravenous histamine base was determined to be 0.04 mg /kg, 5 mg /kg of AH-42 given intraperitoneally 15 minutes previously permitted survival of animals given 60 times the LD<sub>50</sub> of histamine intravenously.

The same or smaller doses of AH-42 administered subcutaneously provided definite protection against anaphylaxis in sensitized guinea pigs subsequently given a shocking dose of antigen intravenously.

Acute toxicity of AH-42 has been determined by various routes on mice, rats, guinea pigs, cats, and dogs, and chronic toxicity tests are in progress.

Results have indicated a favorable therapeutic index.

In doses below 1 mg/kg intravenously, no significant effects on blood pressure were noted.

The excretion and retention of nonprotein nitrogen (NPN) in animals poisoned with uranium. A. ROTHSTEIN, D. DITTMAN, H. BERKE, J. T. MINOR (introduced by Raymond M. Bieter). *Division of Pharmacology and Toxicology, Dept. of Radiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, New York.* Within a day or two after exposure of animals to toxic levels of uranium dusts, there is a decreased rate of excretion of NPN, followed after a similar interval by an increase in the NPN of the blood. Urea and creatinine nitrogen follow the same course of events, but creatine and amino acid nitrogen do not. There is a rise in creatine nitrogen in the urine which only appears when there is a rise in blood NPN. However, rate of the urinary amino acid nitrogen (AAN) excretion is increased in cases of mild uranium poisoning where there is no increase in blood NPN. The increased excretion of AAN is one of the most sensitive early tests of poisoning (especially in rabbits) whereas the increase in blood NPN occurs much later and is a sign of more severe injury. A more satisfactory test than the excretion rate of AAN is the ratio of urinary AAN to creatinine nitrogen (CN). The AAN/CN ratio remains constant in control animals, but increases in from 1 to 5 days after uranium exposure depending on the dose, and remains high if exposure is continued over a 5 week period. The ratio is roughly proportional to the intensity of the exposure. The increased AAN excretion in uranium poisoning is renal in origin and is not accompanied by an increase in blood AAN.

**Biological properties of a soluble derivative of riboflavin.** JACOB SACKS, KARL SCHOEN (by invitation), and S. M. GORDON (by invitation). *Research Labs. of Endo Products, Inc., Richmond Hill, New York.* A series of methylol derivatives of riboflavin has been prepared, the members of which are much more soluble in water than the parent substance. Studies of the riboflavin activity of these substances were made by the microbiological method, and on the basis of these, one was selected for more complete investigation.

This substance contains 82.6 per cent equivalent of riboflavin as determined by nitrogen content and photofluoremetric assay, and is soluble in water at room temperature and pH 7 to the extent of 8 per cent. On a weight basis, it is one third as effective as riboflavin in supporting the growth of *L. casei* (these microbiological assays were carried out by Mr. E. Gottesman).

By the rat growth method of assay, the material

has been found to be about two thirds as effective as riboflavin, on a weight basis.

The relatively high solubility in water has permitted the determination of the acute toxicity. The  $LD_{50}$  in young rats, by intravenous injection is about 700 mg per kg. In mature rats, the  $LD_{50}$  by intravenous injection is about 300 mg per kg. In rabbits, the  $LD_{50}$  by this same route is about 75 mg per kg.

The chronic toxicity is apparently quite low. Young rats fed on a diet which furnished approximately 1 gram per kg per day, showed growth equal to the control group over a two month period.

Further studies of the biological properties of this substance are in progress.

**Investigation of the psycho-chemical basis of visual hallucinations produced by mescaline.** KURT SALOVON, THOMAS THALE and BEVERLY WESTCOTT GABRIO (introduced by A. Gilman). *Dept. of Neuropsychiatry, Washington Univ. School of Medicine, Saint Louis, Missouri.* Mescaline (3,4,5 trimethoxyphenylethylamine) produces hallucinations in man. The foremost action of the drug is probably due to a stimulation of the higher brain centers, especially those concerned with vision.

This is a report of the metabolic fate of mescaline in man and an attempt to correlate the biochemical data observed with psycho-physiological changes occurring in the subjects after ingestion of the drug. With the methods employed, it was hoped to arrive at a better understanding of the physiological basis of visual hallucinations produced by mescaline.

Mescaline sulfate (200, 300 and 400 mg respectively) was given orally to six patients, 5 schizophrenics, and one psychoneurotic who served as the "normal" control. Urine was collected at intervals for eighteen hours, and the excretion product measured by the estimation of methoxy groups, following Zeisel with slight modifications. In all the cases observed the hallucinations occurred before the peak of the urinary excretion curve had been reached. However, in the control patient, the hallucinations were more vivid and extended over a longer period of time. The excretion product was chemically investigated.

Color vision was measured before and after medication with a flicker fusion apparatus. Changes in the perception of color occurred in mescalinated patients, particularly in the green region of the spectrum.

Visual imagery was measured with a test previously described by Cohn. A change in the response to imagery testing has been observed under the influence of mescaline. We therefore, suggest that mescaline acts selectively on the visual mechanism altering not only the perception of color but

also more central processes necessary at one level for the organization of form and at a higher level for recognition and imagery

A quantitative theory how digitoxin congeners act on hypodynamic myocardium WILLIAM T. SALTER, WALLACE F. WHITE (by invitation), and ELIZABETH M. ACKERMAN (by invitation) *Laby of Pharmacology and Toxicology, Yale Univ School of Medicine, New Haven, Connecticut* After prolonged stimulation the response of the isolated papillary muscle of the cat's right ventricle was studied when exposed to pure glycosides (especially ouabain) dissolved in Krebs-Hensleit solution. The data have been reported by White, Belford and Salter. The time factor was minimized by recording equilibrium-responses in a steady state. The idealized "cardiac glycoside," G, shows a maximal stimulating effect when log-concentration equals unity =  $\log 10$ . The myocardium dies when  $\log\text{-concentration} = 1.3$  or  $\log 20$  (micrograms %) approximately. The "therapeutic" effect follows the equation  $\log G = 0.5 + 0.5 \log [R/(1-R)]$ , where R signifies the amplitude of contraction expressed as per cent of the maximal. The "toxic" decline follows the equation  $\log G = 1.15 = 0.15 \log [(1-R)/R]$ . Certain actual glycosides follow these equations except that  $\log G$  becomes  $\log G + M + a$ , where M = minus log potency and  $a$  is characteristic of the individual sample of myocardium used.

It is convenient to assign to ouabain (11% water) the arbitrary value  $M = 0.285$ , so that  $E D_{50}$  equals 1.0. Then its maximal log-concentration reads 1.29 and complete toxicity occurs at 1.59. Other glycosides are displaced horizontally, but in parallel fashion, along the logarithmic abscissa which shows the concentration of glycoside in the mammalian Ringer's solution.

The hypodynamic myocardium will not respond to a given concentration of glycoside unless its degree of "fatigue" lies below the threshold of amplitude corresponding to the particular log-concentration concerned. The quantitative relationships can be explained, tentatively, by assuming the combination of the glycoside with an effector mechanism of structure in the cell. Further combination impeded the normal action, thus inducing "toxicity" [Work aided by grants from the Life Insurance Medical Research Fund and Navy contract N6ori-44, Task Order #VI].

Studies on the 8-aminoquinolines 2. The effects of plasmodid on the central nervous system. IAN G. SCHMIDT (by invitation), and L. H. SCHMIDT, *College of Medicine, Univ of Cincinnati, and the Christ Hospital Inst of Medical Research, Cincinnati, Ohio*. In the preceding report (Federation Proceedings Vol 6, p 369), it was indicated that plasmodid, administered to the rhesus monkey, induced a series of striking neurological dis-

turbances. This report deals with the intensity and character of these changes with particular emphasis on neuroanatomical findings.

In acute intoxication, where death occurred within 18 to 48 hours, there was almost complete obliteration of all cells in the cochlear, vestibular, cerebellar, abducens, trochlear, and oculomotor nuclei. There was also drastic destruction of cell groups associated with these nuclei in ascending and descending pathways. The general picture, that of greatly enlarged perineuronal spaces either empty or containing shrunken remnants of neurones, indicated extreme swelling of cell bodies followed by rapid shrinkage.

In severe chronic intoxication, extending over a period of two to four weeks, the lesions involved the areas indicated above and practically all pathways in the brain stem and striatum. In the cord, the column of Clarke and at least some of the anterior horn cells were involved. In the cerebral cortex the medium sized pyramidal cells in motor areas showed slight changes.

In low grade chronic intoxication more restricted lesions were found. The changes were limited to the nuclei of nerves III, IV, VI, and VIII, the cerebellar nuclei, the lateral cuneate nucleus, the column of Clarke and a very few anterior horn cells. Most cell groups associated with the above nuclei remained normal. [Based upon work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Christ Hospital Institute of Medical Research.]

On the pharmacology of paludrine. L. H. SCHMIDT, HETTIE B. HUGHES (by invitation), and CARL C. SMITH (by invitation) *Christ Hospital Inst of Medical Research, Cincinnati, Ohio*. The pharmacological properties of paludrine have been studied in the rat, dog and monkey. Comparison has been made with quinine, quinaerine, and chloroquine.

When administered to the above animals, daily, over a 60 day period, paludrine had approximately the same or slightly greater toxicity than quinaerine and chloroquine and from 10 to 25 times the toxicity of quinine. No specific reactions occurred in the rat. In the dog paludrine administration induced copious salivation, loss of appetite, extreme cachexia, and cardiac arrhythmia. Symptoms similar to these, except for salivation, were encountered in the monkey. Except for diffuse inflammation of the stomach and intestinal mucosa, gross pathological changes were absent.

Experiments with dogs and monkeys showed that paludrine, like quinine, chloroquine and quinaerine is completely absorbed from the gastrointestinal tract. Absorption of paludrine was somewhat slower than that of these other drugs. In single dose experiments, peak plasma levels of



paludrine occurred approximately 2 to 4 hours after ingestion of the drug. These levels were sustained for 2 to 6 hours, then declined to less than detectable concentrations within another 12 to 18 hours. In single dose experiments there was poor relationship between plasma levels of paludrine and dosage. In chronic experiments, however, dose and plasma level were correlated closely. In such experiments there was no tendency for paludrine to accumulate in the plasma as is the case with quinaerine and chloroquine. On the same dosage of paludrine the monkey had consistently lower plasma levels than the dog.

**Studies on the 8-aminoquinolines** 1. The toxicities of pamaquine and plasmocid in different animal species. L. H. SCHMIDT, CARL C. SMITH (by invitation), HETTIE B. HUGHES (by invitation), and CATHERINE CARTER (by invitation). *Christ Hospital Inst of Medical Research, Cincinnati, Ohio*. Pharmacological studies on pamaquine and plasmocid formed part of the investigations of the 8-aminoquinolines carried out during the recent antimalarial program. These studies encompassed experiments in the rat, dog, and rhesus monkey.

Quantitative differences in the toxicities of pamaquine and plasmocid were observed in all three experimental animals. In each, plasmocid exhibited greater toxicity, one and one half times in the rat, and approximately four times in either dog or monkey. Neither 8-aminoquinoline produced distinctive reactions in the rat. In the dog a variety of reactions occurred, including cyanosis, methemoglobinemia, bilirubinemia, severe abdominal cramping, loss of appetite, ictericia, cardiac arrhythmias, loss of pupillary reflexes, divergent strabismus associated with relaxation of the nictitating membrane, and copious salivation. These reactions characterized intoxication with either pamaquine or plasmocid, although some were better developed with plasmocid.

The reactions of the rhesus monkey to the two compounds were markedly different, pamaquine affected primarily the hematopoietic system, whereas plasmocid affected the central nervous system. Thus the principal manifestations of pamaquine intoxication included anemia, methemoglobinemia, bilirubinemia, and a profound depression of myeloid activity in circulating blood and bone marrow. In contrast to this plasmocid intoxication was characterized by hyperesthesia, nystagmus, loss of pupillary reflexes, loss of vision, dysbasia, dysergia, dysmetria and in some animals paralysis of the lower limbs. These neurological reactions were associated with lesions in the nuclei of cranial nerves III, IV, VI, and VIII and associated cell groups. The reactions to pamaquine were reversible, those to plasmocid were irreversible. [Based upon work done under a contract

recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Christ Hospital Institute of Medical Research.]

**Comparative "antihistamine" action on gastric secretion** A. M. SCHOEN (introduced by P. K. Knocfel). *Univ of Louisville*. Demonstration of quite specific "antihistamine" activity on smooth muscle suggests use in control of gastric secretion. The possibility of predicting gastric secretory antihistamine activity in man from other data was studied by comparing in the same person several substances whose action on smooth muscle, and other properties, was known. Atropine and three synthetic substances were used, nine comparisons in seven subjects being made with a method that permits quantitative determination of the volume of gastric secretion, its acidity and peptic activity. Histamine was injected, after the other agents. The synthetic agents had a carboxyethyl diethylamine side chain attached to (I) fluorene, (II) xanthene, and (III) dihydroanthracene nuclei. Compared with atropine, the synthetic agents were (I) 4, (II) 10, (III) 80 times as effective as histamine antagonists on intestinal smooth muscle. In gastric secretory antihistamine activity, atropine was by far the most effective. Compounds II and III were more active than I, but II was more active than III. Therefore, comparative activity of substances in preventing human gastric secretion in response to histamine is not predictable from antihistamine comparisons made on other tissues.

**Experimental chemotherapy of schistosomiasis** 1. Methods and conditions for drug testing. MAXWELL SCHUBERT (by invitation), and ARTHUR C. DEGRAFF. A laboratory method has been worked out for the screening of drugs for use against schistosomiasis, using white mice as host. Colonies of the snail *Australorbis glabratus* were kept and infected with miracidia hatched from eggs in stools of hamsters infected with *S. mansoni*. Cercariae from these snails were collected, counted and injected intraperitoneally into white mice at a level of 140 cercariae per mouse. During the period eight to twenty weeks after injection of cercariae, 92% of the mice were found to be infected, an average of 11 worms were found per mouse, in the mice the worms were found on the average to be 25% in the liver, 25% in the portal vein and 50% in the mesenteric veins, and 80% of the worms were paired. The distribution curve relating the number of mice with the actual number of worms found in individual mice is presented and discussed. This curve has an unusual shape with a maximum number of mice having no worms and then tapering off so that almost no mice have more than thirty worms.

The influence of these findings on drug testing

and on the quantitative comparison of drug effects is pointed out. Because of the limited confidence that can be placed in average worms found per mouse, when only small groups of mice are used to test drugs of weak or questionable effect, other objective criteria recommended are (1) distribution of worms found in the mice and (2) percentage of worms paired. The advantage of holding mice two weeks after treatment before autopsy in order to observe permanent damage to worms is also pointed out.

**Studies on the mechanism of drug resistance in trypanosomes** F W SCHUELLER (introduced by E M K Geiling) *Dept of Pharmacology, Univ of Chicago*. Trypanosomes when made resistant to a given amino or unide substituted phenyl arsenoxide, as well as to certain basic dyes such as acriflavine, show resistance to many other basic substituted, but not to neutral substituted, phenyl arsenoxides. This suggests that the mechanism by which trypanosomes acquire resistance to the arsenicals may involve the development of resistance to the basic (or acidic) groups on the phenyl arsenoxide molecule and not to the arsenoxide group. The indication that drug resistance in these cases may be resistance only to groups having a certain polarity (either + or -) has suggested that the actual resistance acquiring process may involve a shift in the isoelectric points of some of the proteins of the trypanosome. By means of the method of Pischinger (1925) for finding the isoelectric points of the constituent parts of cells through their stainability with acidic and basic dyes over various pH ranges, it has been possible to reveal differences in the stainability of strains of normal and drug resistant trypanosomes of the same species, thus indicating possible differences in the isoelectric points of their constituent parts.

**Further observations on the pharmacology of dolophine** C C SCOTT, K G KOHSTÄDT (by invitation), I B ROBBINS (by invitation), and F W ISRAEL (by invitation) *Eli Lilly and Company, Indianapolis*. Previously, Scott and Chen (J Pharmacol & Exper Therap 87 63, 1946) reported no tolerance to analgesic action developed when dolophine was administered to dogs in doses of 2 mg intraperitoneally for 28 days (All doses in this report are per kg.) In the present study, larger and more frequent doses were given to rats and dogs.

Dolophine was injected intraperitoneally into rats for 26 days in single doses of 5 mg daily. The average duration of analgesia decreased from 116 minutes on the first day to 31 minutes on the 26th day.

Complete tolerance to analgesic effect of 5 mg of dolophine was established in 2 dogs after receiving the drug for 33 days. Four dogs were started

on 5 mg daily and the dose gradually increased to 40 mg per kg. One dog survived only 14 days and a second animal died on the 32d day, both having developed partial tolerance. The 2 surviving dogs showed no withdrawal symptoms, except moderate increase of heart rate, and, in 1 animal, a slight rise of body temperature.

Intestinal motility studies in trained, unanesthetized dogs revealed only a spasmogenic action following either dolophine or demerol. This occurred even when motility was stimulated by eserine. In contrast, in the same experiments, striking inhibition followed atropine.

Quantitative studies were made in dogs and humans of the degree of respiratory depression caused by dolophine. Various stimulating drugs were tested as antidotes to this effect.

**Some pharmacological actions of the diamidines** LLOYD D SEAGER *Dept of Pharmacology, Woman's Medical College of Penna*. Stilbamidine, Propamidine and Pentamidine injected into the dorsal lymph sacs of frogs in doses of 400 mg per kg produce progressive depression of respiration and muscular activity. Death occurs within 2 to 4 hours. Systolic standstill of the heart was usually found, while the stomach and other smooth muscle structures examined were relaxed.

A curara like action was observed with the compounds on the skeletal muscle using the ligated leg technique. No evidence of sensory depression was found either on local application of the drug to the skin or by injection of the drug. Doses of 150 mg per kg or less produced by slight effects on the muscular activity and all animals survived.

The isolated rat uterus showed little or no changes when the drugs were added to the bath in concentrations of 1:50,000 or less. In concentrations of 1:10,000 to 1:25,000 a depression of tone and often a depression of rate and amplitude was observed. [Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.]

**Prolonged administration of goitrogenic compounds to dogs** JOSEPH SIFTER *Wyeth Inst of Applied Biochemistry, Philadelphia, Pa*. Three of four litter mate female dogs one month old, each weighing approximately 15 kg, received goitrogenic drugs 5 days a week for 6 months. The fourth received no medication. The daily doses per kg of body weight were thiouracil 5 mg, bisacetyltaminophenylselenium dihydroxide 5 mg and 25 mg. The dog receiving thiouracil and the dog receiving the higher dose of selenium compound were retarded in growth and the latter dog gradually took on the appearance of a pituitary dwarf with undeveloped mammary glands and vulva. Deformation in these two dogs was abnormal, and x-rays of the long bones revealed delayed growth and delayed epiphyseal closure.

At autopsy the untreated dog weighed 10 kg, the dog that had received the low dose of selenium compound weighed 11.9 kg, the dog that had received thionureil weighed 8.4 kg, and the dog that had received the high dose of selenium compound weighed 4.9 kg. The uterus and ovaries in the litter two dogs were small (body weight basis) and the adrenals somewhat enlarged. The histological examination revealed that the thyroid gland was essentially normal in all the dogs. The uterus was atrophied and the ovaries undeveloped in the affected dogs. The anterior pituitary gland in these two dogs showed a decrease in the chromophobe basophil acidophil ratio.

**A study of 2-methylaminoheptane** F. L. SHAFFER (introduced by P. K. Knoefel) *Univ. of Louisville*. In man, oral doses of 200-300 mg of the hydrochloride give rises in systolic (15-20 mm Hg) and diastolic arterial pressures, with return to normal in about 2½ hours. A comparable rise but of longer duration, is produced by ¼ to ½ the dose of desoxyephedrine. A comparable rise, but more prompt and briefer than after oral administration is produced by subcutaneous injection of ½ to ¾ of the oral dose of 2-methylaminoheptane. Stimulation of the central nervous system seen with desoxyephedrine, did not occur with 2-methylaminoheptane. In anesthetized dogs 2-methylaminoheptane is about ½ as active a vasoconstrictor agent as desoxyephedrine, but tachyphylaxis is less with the former. The acute lethal toxicity of 2-aminoheptane, 2-methylaminoheptane, and desoxyephedrine is about the same for intravenous injection but by subcutaneous injection the last compound is more toxic than the other two, which are equally toxic. Chronic toxicity was studied by incorporation of the drug in the food of rats. There was no interference with growth of male or female rats at an average intake of 10 mg/kg/rat/day (of drug base). Female rats at 23 showed some impairment of growth, male rats at 67 showed none. A group of both sexes at intake of 122 showed impairment of growth, but not of fertility. This daily dose is ½ of the single fatal dose. No rats showed histological evidence of damage to tissues.

**Respiratory excretion of methyl alcohol by white rats** T. E. SHEA, JR. and C. H. HINE (introduced by H. A. Anderson) *National Naval Medical Center, Naval Medical Research Inst., Industrial Hygiene and Toxicology Facility*. The ratio of excretion by respiration and disposal of methanol by metabolism is controversial. In this study, the elimination of methanol by way of the respiratory system was determined colorimetrically by oxidation of the collected vapors in an acid dichromate reagent. The vapors were collected in a face mask and carried by a stream of ambient air into the oxidizing agent.

White rats received 9.6 grams of methanol per kilogram of body weight by stomach tube. Samples of the expired air were collected for eight hours a day on successive days until the dichromate was no longer reduced.

Results of sampling were calculated for periods of twenty-four hours. Average results show 12 per cent exhaled in the first twenty-four hours, 10 per cent in the second twenty-four hours, 6 per cent in the third twenty-four hours, and less than a total of 4 per cent in the fourth, fifth, and sixth twenty-four hour periods.

When eight per cent carbon dioxide in oxygen was inhaled, no change in the total recovery of methanol was observed though there was an initial transitory increase.

Analysis of the brains of animals killed after the fifth period showed no appreciable methanol.

Only about 30 per cent of the total methanol ingested could be accounted for in the expired air, leaving 70 per cent to be disposed of by metabolism or other routes of excretion.

**The effects of digitalis on electrolytes of heart muscle** THEODORE R. SIERRROD (by invitation) and W. J. R. CAMP *Dept. of Pharmacology Univ. of Illinois College of Medicine Chicago 13*. Twenty-one normal dogs were injected intravenously with Tincture of Digitalis (0.1 cc per kgm of body weight) diluted with an equal volume of physiological saline. Immediately after death muscle from each of the four chambers of the hearts was analyzed for H<sub>2</sub>O content, total N, chlorides, Na, K, Mg, total P, Fe and Ca. The results were compared with those of similar analyses made on hearts of nineteen untreated dogs. Right and left trabecular muscle showed an increase in Na but no significant changes in the other electrolytes. Water, total N, P, Mg, Fe and chlorides were unaltered by digitalis in any of the heart muscles. Ten dogs receiving amounts of alcohol equivalent to that administered in the tincture showed no significant changes from the normals.

**Acute vascular tolerance to morphine, demerol, and 1,1-diphenyl-1-(dimethylamino-isopropyl)butanone-2 (amidone) in the dog** F. L. SHIDEMAN and H. T. JOHNSON (by invitation) *Dept. of Pharmacology Univ. of Michigan*. Morphine sulfate (2-4 mg/kg), Demerol hydrochloride (5 mg/kg), or Amidone hydrochloride (2 mg/kg) all, when administered intravenously to dogs under pentothal barbital anesthesia produce an acute fall in arterial pressure which varies in degree and duration. This period of hypotension is characterized by (1) an acute transient fall in arterial pressure with partial recovery in 2-5 minutes merging into (2) a less severe but greatly prolonged period of hypotension from which gradual recovery usually occurs in 30 to 180 minutes.

Following repeated administration of morphine

complete tolerance to the hypotensive action (1 & 2) of this drug may be produced (Schmidt and Livingston, *This Journal* 47 411, 1933), with Demerol partial, but never complete, tolerance to both (1) and (2) is developed, with Amidone no tolerance to (1) but complete tolerance to (2) may be induced

Morphine tolerant animals show a) partial crossed tolerance to (1) and (2) with Demerol and b) complete tolerance to (2) but no tolerance to (1) with Amidone. Repeated administration of Demerol or Amidone does not confer any crossed tolerance to morphine [*Supported by a grant from Parke, Davis and Company*]

Urinary excretion of cetyl pyridinium R. SHORE (introduced by P. K. Knoefel) *Univ of Louisville*. Some quaternary ammonium compounds are known to be excreted in the urine. If this is the case with cetyl pyridinium, a urinary antiseptic action might be expected. Cetyl pyridinium added to dog urine can be recovered as the Remicke salt, determined gravimetrically as  $\text{Cr}_2\text{O}_3$ . Cetyl pyridinium chloride was given orally to dogs, 100-150 mg per kg, and urine collected for three days. No cetyl pyridinium remickate could be recovered from these urines. Only a small amount could be recovered from the feces, indicating that most had been absorbed. Administered pyridine is known to be excreted as methyl pyridinium, this was confirmed, by precipitation as phosphotungstate and isolation as chloroplatinate. No methyl pyridinium could be isolated from urine after administration of cetyl pyridinium.

A laboratory investigation of intravenous oxygen therapy R. A. SIMSON (introduced by O. S. Orth) *Dept of Anesthesiology, State of Wisconsin General Hospital, Madison*. Recent encouraging clinical reports on the use of oxygen intravenously justify further investigation. Dosages used in most previous laboratory studies (1 to 3 cc/kg/min) have exceeded amounts of oxygen used clinically (0.1 to 0.25 cc/kg/min). In this investigation the effects of clinical dosages have been studied on dogs.

Symptoms noted by others, viz, tachypnea, orthopnea, and decreased blood oxygenation, were seen even with the use of clinical amounts. An attempt was made to determine the mechanism by which clinical improvement might be accomplished since the quantities of oxygen so administered are inadequate to significantly add to the respiratory intake of oxygen.

The previously observed elevation of right ventricular pressure has been confirmed. Increased right ventricular output was not found and thus the interesting hypothesis that clinical improvement from intravenous oxygen resulted from such an effect was not substantiated.

Using blood oxygenation as a criterion, bene-

ficial results were not demonstrated with administration of clinical amounts. Blood oxygen content was almost invariably reduced. In animals in which hypoxia was produced previously to create a need for oxygen, a further reduction of blood oxygenation was found upon intravenous oxygen administration.

The greatest benefit from intravenous oxygen would be expected in pulmonary edema which is not of cardiac origin. No improvement occurred in the condition of three dogs in which pulmonary edema was produced by 50 mg/kg of alphanaphthylthiourea (ANTU) given intraperitoneally. All the animals died in less than 12 hours.

Further studies of the treatment of shock with intravenous oxygen are planned.

Studies on the 8-aminoquinolines 3. On the relations between structure and pharmacological activities C. M. C. SMITH (by invitation) and L. H. SCHMIDT *Christ Hospital Inst of Medical Research, Cincinnati, Ohio*. More than one hundred 8-aminoquinolines, synthesized during the recent antimalarial program, have been examined for pharmacological characteristics in the monkey. These compounds produced three distinct types of toxic reactions: (1) depression of the myeloid elements of peripheral blood and bone marrow, (2) highly localized degenerative changes in the central nervous system associated with functional derangement, (3) effects on the heart and circulation. These have been designated as pamaquine-like, plasmodium-like and atypical reactions respectively.

The type of toxic reactions induced depended primarily upon the structure of the side chain, and with but few exceptions was independent of nuclear substituents. Thus all compounds in which the terminal nitrogen of the side chain was unsubstituted produced pamaquine-like reactions. In compounds with one or two alkyl groups on the terminal nitrogen, the type of reaction usually was dependent upon the number of methylene groups separating the nitrogen atoms in the side chain. With four exceptions, plasmodium-like reactions were obtained with compounds having two or three methylene groups. Pamaquine-like reactions were obtained with derivatives having methyl-butyl, hexyl or longer methylene chains. With side chains containing four or five methylene groups, the reactions seemed to be mixed. Atypical reactions, i.e., effects on the heart and circulation, characterized compounds in which 2 piperidyl groupings replaced the terminal alkylamino groups [*Based upon work done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Christ Hospital Institute of Medical Research*].

The chemotherapeutic action of streptomycin

and sulfone derivatives in experimental tuberculosis M I SMITH, WU T McCLOSKEY, E L JACKSON (by invitation) and HUGO BAUER (by invitation) *Division of Physiology, National Inst of Health, Bethesda, Md* Previously published data (Smith and McClosky, Pub Health Rep 60 1129, 1945, Smith, McClosky and Emmart, Proc Soc Exp Biol & Med 62 157, 1946) have shown that combined therapy with streptomycin and sodium p,p' diaminodiphenylsulfone N-N'-didextrose sulfonate (promin) in experimentally infected guinea pigs gave a chemotherapeutic effectiveness greater than the sum of effects from the individual components Since then other sulfone derivatives have been tested, alone and in combination with streptomycin, with the object of developing a sulfone derivative less toxic and if possible more effective than promin, and to determine the possibility of potentiation with streptomycin

Four compounds, including promin, have been studied to date The compounds are

- 1 Promin
- 2 Sodium salt of 4 amino-4' galacturonylamino-diphenylsulfone (galacturonyl)
- 3 4-Amino-4' succinimidodiphenylsulfone (succinimido)
- 4 4-Amino-4'-n propylanunodiphenylsulfone (n-propyl)

The results of this study are summarized in the following table, the term chemotherapeutic effectiveness being used to denote the ratio of the extent of tuberculous involvement in a group of infected controls and of a group similarly infected and treated

Strepto- mycin (mg/kg /day)	Sulfone	Chemo- thera- peutic effective- ness	% free from lesions	% mortality in relation to controls
10-15	0	5.2	15	0/65
40	0	14.4	40	0/90
0	Promin	2.4	5	15/65
0	Galacturonyl	2.7	5	70/95
0	Succinimido	1.8	0	50/90
0	n Propyl	3.7	0	50/90
10-15	Promin	20.0	65	0/65
20	Galacturonyl	27.0	75	5/95
20	Succinimido	18.2	55	5/90
20	n Propyl	28.6	72	0/90

The data indicate (1) greater chemotherapeutic efficacy for streptomycin than for any of the sulfones tested, (2) of the several sulfones tested the n propyl derivative appears the most effective, (3) potentiation of action when streptomycin is used in combination with the sulfones

The hydrolysis of acetylsalicylic acid by animal tissues PAUL K SMITH, HERBERT A HAND

(by invitation) and ROBERT J MADDEN (by invitation) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* This is a continuation of an observation made some time ago that the metabolites of aspirin are apparently identical with those of sodium salicylate and that aspirin is rapidly hydrolysed by human subjects to free salicylate

When aspirin is given intravenously to dogs, it is rapidly hydrolyzed to free salicylate Normal human plasma hydrolyzes aspirin fairly rapidly, a dilute solution being almost completely hydrolyzed within three hours The tissues of rats that contain the largest concentrations of the enzyme are the liver and kidneys, each containing at least 5 times as much per gram as does plasma

The crude enzyme, as prepared from dog liver, is very water soluble, not being precipitated readily even by saturated sodium sulphate It has an optimal activity in the crude state of approximately pH 6 to pH 6.5, depending somewhat upon the buffer salt employed It was not appreciably inhibited by the addition of sodium cyanide, sodium fluoride or mercuric chloride It is however, readily destroyed by heating to 70° for one hour It does not hydrolyze the acetyl group of substances such as acetylated para aminobenzoic acid or acetanilid but it is very active against ethyl butyrate When preparations of the crude enzyme are prepared by the methods outlined in the literature for liver esterase both ethyl butyrate and aspirin are hydrolyzed at a rate approximately parallel with that obtained with the crude tissue extract Thus the evidence indicates that the enzyme may be similar to ordinary liver esterase [Supported by a grant from the Inst for the Study of Analgesic and Sedative Drugs]

The effects of di-isopropyl fluorophosphate and physostigmine on the sympathetic ganglia FREDERICK SPERLING (by invitation), ALEXANDER G KARCYMAR (by invitation) THEODORE O KING (by invitation) and THEODORE KOPANYI *Dept of Pharmacology and Materia Medica, Georgetown Univ, School of Medicine* The effects of DFP and physostigmine upon the pressor action of acetylcholine were compared in atropinized dogs The standard dose of 0.5 mg/kg of acetylcholine has no pressor effect in the absence of esterase inhibitors The lowest effective dose of DFP appeared to be between  $2 \times 10^{-6}$  and  $5 \times 10^{-6}$  mol/kg, whereas that of physostigmine between  $5 \times 10^{-8}$  and  $8 \times 10^{-8}$  mol/kg The plot relating DFP concentrations and the pressor effects of acetylcholine was fairly linear until the dose of DFP reached  $5 \times 10^{-6}$  to  $10^{-4}$  Then it became asymptotic, no further increases of pressor effect being evident with doses larger than  $1.5 \times 10^{-4}$  mol/kg In some dogs the slope of the linear part of the curve may be steeper With physostigmine a

linear increase in pressor effects was obtained with doses from  $5 \times 10^{-8}$  to less than  $2 \times 10^{-6}$  mol/kg, the curve presenting a plateau for values from  $2 \times 10^{-6}$  to  $4 \times 10^{-6}$  mol/kg and a subsequent decline. It should be pointed out, therefore, that physostigmine is about 100 times more potent than DFP under the above experimental conditions. This fact and the different shapes of the pertinent curves are additional indications of the different nature of their action on the nicotinic effects of acetylcholine. Finally, it is suggested that the magnitude of the pressor effect of acetylcholine in atropinized animals and in the presence of varying concentrations of DFP may be used as an indication of specific cholinesterase content (cf. Koppányi, Sperling and King, *Anat. Record* 98:5, 1916).

**Studies of gastric motility on ulcer patients before and after vagotomy--effect of parasympathomimetic drugs.** I. F. SREIN, JR. (by invitation), F. SRIENMANN, and KARL A. MEYER (by invitation) *Cook County Hospital and Hektoen Inst. for Medical Research.* Decrease of gastric motility and acidity is one of the goals endeavored to produce by vagotomy. The decrease in motility, however, may at times be so great as to produce an actual retention for 1-6, or more, hours with resultant symptoms of epigastric fullness, belching, foul breath, and occasionally actual distress. Rarely, this lessened motility may lead to acute dilatation of the stomach. Close observation of 15 patients following vagus section has shown that many need some relief for the gastric retention, particularly during the post operative period, and in some cases for several months.

The effect of various parasympathomimetic drugs for relief of this gastric atony was studied in a small series of cases. Gastric motility was recorded kymographically by means of a balloon in the stomach before and after vagotomy. Results of this study are as follows:

Prostigmin, 30 mg orally and  $1^{-1}$  mg subcutaneously, produced little or no increase in gastric motility. Mecholyl, 200 mg orally, had questionable effect on gastric motility. Doryl, 0.25 mg subcutaneously, or 2 mg orally produced marked increase in gastric motility. The effect was quicker after the subcutaneous injection. Urecholine, 10 g orally, produced marked increase in gastric motility.

While this series is comparatively small the study indicates that most patients with vagotomy will require some medication for relief of gastric atony. Urecholine and Doryl appear at present to be the two most useful agents for this purpose.

**Toxicity of uranium dusts.** H. E. STOKINCLER, EUGENE ROBLERIS, CHARLES J. SPILGL, A. ROHSILIN, J. J. ROHLERWILL, GEORGE SPRACUL, JR. (introduced by H. B. Haag) *Division of Pharma-*

*cology and Toxicology, Dept. of Radiology, School of Medicine and Dentistry, The Univ. of Rochester, Rochester, N. Y.* Probably the largest experimental program of heavy metal toxicology has been conducted involving approximately one half hundred 30 day acute studies and a dozen, year long, chronic studies of twelve uranium dusts. The levels that constitute toxic, borderline, and safe exposures for animals have been established.

The dust concentrations of acute studies involved a hundred fold range (20 to 0.2 mg/m<sup>3</sup>). Levels of chronic studies were as low as 0.05 mg/m<sup>3</sup>. Thus, levels above, at, and below the interim choice of maximal allowable exposure concentration (0.150 mg/m<sup>3</sup>) set for industry were thoroughly tested.

Numerous criteria of toxicity were used that comprised in addition to the usual observations of mortality, weight response, and histologic changes, newly developed sensitive tests of urinary catalase and amino acid nitrogen as measures of renal function. As a result of the study of these, it was found that uranium dusts may be grouped in two categories: (1) the soluble, toxic dusts, UF<sub>6</sub>, UO<sub>2</sub>F<sub>2</sub>, UCl<sub>4</sub>, and U-nitrate and (2) the more insoluble less toxic dusts, U<sub>3</sub>O<sub>8</sub>, UO<sub>2</sub>, U<sub>2</sub>O<sub>3</sub>, UO<sub>3</sub>, and Na and NH<sub>4</sub> diuranates and ores. Levels of 20 mg/m<sup>3</sup> of the soluble dusts were generally fatal, most species incurring severe renal and frequently pulmonary damage in acute exposures. Most of these materials were occasionally fatal and produced uniformly slight renal damage in the more susceptible species even at 0.2 mg/m<sup>3</sup>.

A year's exposure to U-nitrate produced no pulmonary damage in the dog or rat at 2 mg/m<sup>3</sup> but did incur moderate renal injury without fatality in both the dog and rat at this level. Most important was the finding of altered cellular structures persisting in renal tubules following repair of initial injury; this was interpreted as evidence of tolerance to uranium rather than as chronic injury.

**The convulsive effects of streptomycin.** HENRY M. SUCKER (by invitation), ROLAND R. LIEBENOW (by invitation) and O. S. ORIN *Depts. of Neurosurgery, Physiology and Pharmacology, State of Wisconsin General Hospital and Univ. of Wisconsin Medical School, Madison.* The toxic effects of streptomycin on the central nervous system have been determined experimentally in rabbits, dogs, and *Macacus rhesus* monkeys. The antibiotic was applied to the frontal, motor or occipital area of the cerebral cortex and was followed by minor and major convulsions of status epilepticus proportions, transient paralysis, and death in some instances. More severe and pronounced reactions followed application of the drug to the motor area. In rabbits 30 mg streptomycin applied to this area produced major reactions in 6 of 10 animals,

and 4 of the 6 having such major reactions died within 4 hours. In puppies 50 mg. caused major convulsive reactions in 3 of 4 animals. In adult dogs 100 mg. streptomycin produced major reactions in the majority of animals. In monkeys 50 mg. produced minor reactions while 75 mg. resulted in major reactions consistently.

Partial and total inactivation of the streptomycin indicated that the antibiotic principle was directly proportional to the convulsive factor. Semi-carbazide HCl 60 mg./cc. and cysteine HCl 400 mg./cc. inactivated the streptomycin solution which originally contained 200 mg. active antibiotic per cc. The cortical stimulating effect of streptomycin was shown by the spread of focal myoclonic seizures to generalized convulsions, by electroencephalographic changes indicative of a grand mal type of seizure, and the cessation and prevention of the seizures by sub-anesthetic doses of barbiturates, which are known to depress cortical function. Histological examination of the meninges and the cerebral cortex revealed changes which paralleled the severity of the convulsive reactions. They consisted chiefly of a loss of normal cortical structure and an increase of glial tissue and widespread perivascular cuffing.

**Toxicity and narcotic action of mono-chloro-mono-bromo-methane with special reference to inorganic and volatile bromide in blood, urine, and brain.** J. L. SVIRBELY, W. C. ALFORD (by invitation), W. F. VON OETTINCEN. *Industrial Hygiene Research Lab., National Inst. of Health Bethesda, Maryland.* The  $LD_{50}$  of mono-chloro-mono-bromo-methane with 7 hours exposure for mice was determined as 15.85 mg./liter counting fatalities occurring during 8 hours, 13.25 mg./liter for 24 hours, 12.89 mg./liter for 48 hours, and 12.03 mg./liter for 72 hours after beginning of the exposure, reflecting the prolonged narcotic action of this compound as compared with di-chloro-methane. With repeated exposure to 5.3 mg./liter the inorganic bromide level in the blood of dogs increased after each exposure and did not return to pre-exposure levels overnight, so that during daily exposures there was a steady increase of the bromide level, at the end of 13 weeks exposure this was of the order of 300 to 360 mg. per 100 cc. of blood. The excretion of inorganic bromide with the urine follows similar patterns. In contrast, the level of volatile bromide in the blood was of the order of 7 to 9 mg. per 100 cc. of blood, but after 17 and 65 hours it dropped to very low values or to zero. At the end of the last repeated exposure 100 grams of brain of dogs, rabbits, and rats contained from 20.9 to 61.5 mg. of inorganic bromide per, but only from 0.25 to 0.82 mg. of volatile bromide. The experiments indicate that following its absorption mono-chloro-mono-methane is rapidly decomposed with formation of inorganic bromide which ac-

cumulates in the blood and to a lesser extent in the brain.

**Effects of diethyl ether, chloroform and cyclopropane on spontaneous cardiac irregularities in the Macacus rhesus.** HENRY M. SUCKLE (by invitation), ROLAND R. LIEBENOW (by invitation), and O. SIDNEY ORTH. *Depts. of Physiology, Neurosurgery and Pharmacology, Univ. of Wisconsin Medical School and State of Wisconsin General Hospital, Madison.* Six monkeys (*Macacus rhesus*) averaging six kilograms in weight have been tested with the anesthetic agents by having control electrocardiograms taken from all three standard leads before induction. During continuous electrocardiographic observation, induction was made with diethyl ether or chloroform by the open drop technique or with cyclopropane by the to-and-fro absorption technique. Lead II electrocardiograms were taken whenever any cardiac irregularities were observed, anticipated or suspected. On subsequent occasions anesthetization was repeated and atropine sulfate 0.5 mg./kg. or dihydroergotamine methanesulfonate (DHE 45—Sandoz) 0.4 mg./kg. was given to block, respectively, the parasympathetic or the sympathetic innervation of the heart.

Increasing severity of cardiac irregularities occurred as ether, cyclopropane or chloroform was used. Four anesthetizations with ether elicited no greater effect than sino-auricular tachycardia. A fifth animal had occasional ventricular extrasystoles. Adrenalin injections (0.0025 to 0.005 mg./kg.) produced no change in cardiac automaticity. All types and degrees of auricular and ventricular disturbances of rhythm were noted on 6 anesthetizations with cyclopropane. Atropine did not prevent them. In two experiments, DHE 45 stopped multifocal ventricular tachycardia. Inconsistent results have followed premedication with this drug, but inadequate dosage may be the factor.

Five animals tested with chloroform in nine experiments uniformly showed multiple types of arrhythmia which in 4 instances were not augmented by adrenalin. Ventricular fibrillation occurred during one induction. Ventricular arrest preceded fibrillation in 2 other experiments.

**Influence of BAL on the acute toxicity of gold salts in mice.** ROLLAN SWANSON (by invitation), JOSEPH NEL (by invitation) and PAUL K. SMITH. *Dept. of Pharmacology, The George Washington Univ. School of Medicine, Washington, D. C.* The protection obtained against the toxic effects of mercuric and arsenic salts with BAL (2,3 dithio-propanol) suggested a study of its effects on the toxicity of gold salts. Accordingly, groups of mice, given single intraperitoneal injections of 40 mg. per kg. or of 60 mg. per kg. of gold sodium thiosulfate, were given daily doses of 10 mg. per kg. of BAL for 8 doses or until death. The larger dose of gold salt killed all the mice when given



alone, but with BAL half of the group survived. In both groups receiving BAL there were significantly fewer deaths than in mice receiving the gold salt alone. Smaller, more frequent, doses of BAL are being used in an effort to increase the protective action. Further studies are planned to determine if the protection is due to an increase in the excretion rate of gold salt. [Supported by a grant from the Council on Pharmacy and Chemistry of the American Medical Association.]

**Validity of laboratory anticonvulsant tests for predicting antiepileptic potency and specificity.** LEWART A. SWINYARD (introduced by Louis S. Goodman) *Dept of Pharmacology, Univ of Utah School of Medicine, Salt Lake City, Utah.* Several common barbiturates were compared with clinically accepted antiepileptics for their relative ability in rats to abolish hindlimb tonic extension in maximal electroshock seizures, and to prevent Metrazol convulsions. Toxic doses ( $TD_{50}$ ) and protective doses ( $PD_{50}$ ) were determined graphically and the protective indices calculated ( $TD_{50}/PD_{50}$ ). Results are tabulated.

Drug	Protective index		Usefulness in epilepsy
	Maximal electroshock*	Metrazol†	
Dilantin	2.4	0	G M Ps M
Mesantoin	11	0.9	G M
Tridione	1.2	1.5	P M
Phenobarbital	3.0	0.9	G M
Mebaral	2.5	2.5	G M
Neonal	1.9	0.8	
Pentothal	1.0	1.4	
Pentobarbital	1.4	0.0	
Delivinal	1.1	0.7	
Amytal	0.9	0.7	
Barbital	0.7	1.1	

\* 60 cycle A C 150 mA, 0.2 sec, corneal electrodes

† 70 mg/kg s.c. G M grand mal Ps M psychomotor, P M petit mal

Barbiturates and hydantoinates effective in grand mal and psychomotor epilepsy all exhibit adequate protection against electroshock. Oxazolidine-2,4 diones effective in petit mal exhibit protection against Metrazol. The significance of Metrazol protection in the barbiturate series awaits elucidation. Apparent lack of clinical usefulness of barbiturates other than phenobarbital and Mebaral is, in general, substantiated by the laboratory data. The ultimate objective of these studies is to determine the validity of laboratory tests for screening potentially useful antiepileptic drugs. [Assisted by a research grant-in aid of the U S Public Health Service.]

The metabolism of para-aminobenzoic acid in patients with diminished liver function. CELIA

WHITE TABOR (by invitation) JUDITH BAILY (by invitation) and Paul K. Smith *Dept of Pharmacology, George Washington Univ School of Medicine, Washington, D C.* Para-aminobenzoic acid was administered to a group of patients with laboratory evidence of liver disease and to a group of controls. The urinary excretion of metabolites of para-aminobenzoic acid was followed at two, four, and six hour intervals using a modification of the technique previously employed by Smith et al (Fed Proc 5 151-155, 1946). The normal subjects were found to excrete over 50 per cent of the administered dose in 4 hours and 60 to 90 per cent in 6 hours. The excreted products were found to be predominantly para-aminohippuric acid and a small fraction was in the acetylated form.

In the subjects with liver dysfunction, less than half of the administered dose of para-aminobenzoic acid could be recovered in the urine. These patients were found to excrete a significantly lower proportion of para-aminohippuric acid, although the absolute amount of the acetylated para-aminohippuric acid was approximately the same as in the controls. In the same subjects an oral hippuric acid test was run at another time. The decreased hippuric acid excretion correlated well with the diminished para-aminohippuric acid. The values in the presence of liver dysfunction appear to be higher than in normal subjects. This finding is being investigated further as a possible liver function test. [Supported by a grant from the Navy Department.]

The action of various cinchona alkaloids on the isolated heart of *Limulus polyphemus*. CHARLES H. TAFT (introduced by G. A. Emerson) *Pharmacology Dept Medical Branch, The Univ of Texas, Galveston and The Marine Biological Lab, Woods Hole, Mass.* Hearts were removed and placed in 250 ml of aerated sea water (isotonic with limulus serum). The anterior end was anchored and the posterior end attached to a heart lever writing on a kymograph drum. The alkaloids added to the bath were all dihydrochlorides in a 2.5% solution in sea water. Each experiment was done on a fresh heart.

Preliminary experiments indicate that of the cinchona alkaloids used ethylapocuinine was the most toxic to the limulus heart as 0.5 ml added to the bath stopped the heart in one minute and that apocinemonine and quinine were the least toxic as they did not stop the heart in one hour. Cinchonine 2 ml, quinine 1 ml, and apoquinine 1 ml stopped the heart in ten minutes or less. Cinchonidine 1 ml, cinchonine 1 ml, quinine 0.5 and 1 ml, quinine 0.25 ml and hydrocinchonidine 1 ml, hydrocinchonine 1 ml, hydroxyethylapoquinine 2 ml, hydroquinine 0.5 ml, and hydroquinidine 2 ml stopped the heart in between 11 and 24 minutes.

In the doses given, with cinchonidine, cinchonine, quinine, quinidine, hydrocinchonine and apoquinine there was an increase in both rate and amplitude before the hearts stopped. With quinine 0.5 ml, apocinchonine and ethylapoquinine there was an increase in rate and fall in amplitude. With hydroethylapoquinine and hydroquinine there was an increase in rate and no change in amplitude. With hydroquinidine and quinine both rate and amplitude were unchanged.

**Comparative hyperglycemic responses of rabbits to injections of levo and racemic epinephrine.** CHARLES H. TAFT (introduced by G. A. Emerson) *Pharmacology Dept., Medical Branch, The Univ. of Texas, Galveston*. Both the levo and racemic epinephrine used were the synthetic epinephrine "suprarenin." The optical rotations of these substances were checked. The blood sugar determinations were made by the Hagedorn-Jensen method.

After intravenous injection of 0.01 mg/kg, in terms of the base, the rise in blood sugar was greater with the racemic than with the levo for the first 45 minutes. At sixty minutes the blood sugar level with the racemic had fallen below the initial level, while with the levo it was practically at the initial level.

Following intravenous injection of 0.05 mg/kg again the initial response to racemic was greater than to levo. For the first thirty minutes the "t" test showed it to be significantly greater. At the 45 and 60 minute intervals the response to racemic is greater, it is not significantly so. At the end of two hours the blood sugar of the racemic animals was below the initial level while in the levo animals it was well above the initial level.

Following the subcutaneous injection of 0.25 mg/kg of the two substances the blood sugar curves were practically the same for the first two hours.

**Speed of hyperglycemic response in rabbits to intravenous injection of epinephrine.** CHARLES H. TAFT and HELEN B. TAFT (introduced by G. A. Emerson) *Pharmacology Dept., Medical Branch, The Univ. of Texas, Galveston*. The rabbits used were all males and were not fed for 24 hours before the experiment. The epinephrine used was the artificial "Suprarenin." 0.01 mg/kg epinephrine in terms of the base was injected into the marginal vein of one ear and samples taken into ovalated watch glasses from the marginal vein of the other ear at intervals of 1, 2, 3, 4, and 5 minutes after injection. Blood sugar determinations were by the Hagedorn-Jensen method.

The mean blood sugar values obtained in mg % glucose and the standard deviation of the mean were: initial  $107 \pm 1.9$ , one minute  $107 \pm 2.7$ , two

minutes  $111 \pm 3.5$ , three minutes  $109 \pm 3.1$ , four minutes  $114 \pm 2.99$ , and five minutes  $119 \pm 3.3$ .

When the "t" test is applied to these figures the following values are obtained: initial and 3 minutes  $t = 0.5889$ , initial and 4 minutes  $t = 2.012$ , and initial and 5 minutes  $t = 3.2631$ . Therefore the probabilities that there is no difference between these time intervals and the initial are: 3 minutes, 0.6, 4 minutes, 0.05, 5 minutes, 0.001.

It is interesting to compare the speed of hyperglycemic response to the intravenous injection of epinephrine with the hypertensive response, the hypertensive response being at most a matter of seconds while the hyperglycemic response takes at least four minutes.

**Toxicology of the synthetic estrogen, dienestrol.** R. S. TEAGUE *Dept. of Physiology and Pharmacology, Medical College of Alabama, Birmingham*. A study of the chronic effects of large doses of Dienestrol has been made in rats and dogs, using Diethylstilbestrol as a standard for comparison.

Although oral assay of Dienestrol performed elsewhere has shown it to be slightly weaker than Diethylstilbestrol, on chronic oral administration we found the two substances to have about the same activity.

Each substance was given orally in propylene glycol to rats for 3 to 14 weeks while controls received the solvent alone. Both estrogens increased the weight of the uterus, sometimes producing pyometra, and decreased the weight of the ovary and male sex apparatus. They always caused enlargement of the pituitary, sometimes of the adrenal, and occasionally of the kidney. The liver was usually enlarged, contained excess glycogen, while the blood sugar remained normal. No degenerative changes were found microscopically in the liver or kidney.

In dogs, the dipropionate of each drug in corn oil was injected intramuscularly. Both caused a fall in the red blood cell count and hemoglobin and a leukocytosis largely reflected in the neutrophils. No fall in platelet count was seen, although this may be due to the effect of the solvent. Death occurred in 12 weeks.

No important differences were found between Dienestrol and Diethylstilbestrol in their actions in rats and dogs. [Aided by a grant from the University Research Committee and the White Laboratories, Inc.]

**Effects of toxins of Clostridium botulinum and Clostridium tetani on acetylcholine synthesis.** CLARA TORDA and HAROLD G. WOLFF *New York Hospital and Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York, N. Y.* Because of the importance acetylcholine may have in the transmission of stimuli at the myoneural junction the effect of the toxins of the "neurotropic" microorganisms (Clostridium

<sup>1</sup> Kindly furnished by the Winthrop Chemical Co.

botulinum and Cl tetani) on the synthesis of acetylcholine was investigated

To ascertain the effect of toxins on the synthesis of acetylcholine a modified method of Quastel, Tennebaum, and Wheatley was used

In the presence of low concentrations of tetanus toxin the synthesis of acetylcholine increased. An increase of 22 per cent was found in the presence of 1 LD<sub>50</sub> (guinea pig), 50 per cent in the presence of 50 LD<sub>50</sub> and 25 per cent with as high as 5,000 LD<sub>50</sub>. With concentrations as high as 10,000 LD<sub>50</sub> some inhibition of acetylcholine synthesis occurred.

The synthesis of acetylcholine decreased in the presence of low (25 per cent inhibition in the presence of 0.1 LD<sub>50</sub> (mouse)) and increasing concentrations of the toxin of Cl Botulinum (Type A and B).

The increased acetylcholine synthesis may contribute to the over excitability of the myoneurial junction observed after injection of the toxin of Cl tetani and decreased acetylcholine synthesis may contribute to the production of "functional paralysis" observed in animals after introduction of the toxin of Cl botulinum.

**Mechanism of relief of pain in sprains by local injection techniques.** JAMES TRAVITT and ALBERT L. BONN (by invitation) *Dept of Pharmacology of Cornell Univ Medical College, New York*. Six acute sprains in human subjects were treated by local infiltration of the traumatized tissues with physiologic saline, and one such case by dry needling alone. The joints involved were the knee, ankle, wrist, and metacarpophalangeal joint of the thumb. The spread of pain induced by insertion of the needle into the exquisitely tender spots in the region of the sprained joint indicated the presence of a trigger mechanism at the site of injury. In 4 of the subjects, complete and permanent relief of pain and disability was secured at once by local infiltration of these trigger areas with physiologic saline, just as by infiltration with procaine in similar cases, in 3, more than one such treatment was required for a permanent result. Since infiltration with physiologic saline or dry needling were effective, interruption of the vicious cycle assumed to be responsible for pain in these cases cannot be attributed to the local anesthetic action of a drug, as has heretofore been ascribed to the effect of procaine.

A plausible explanation of these phenomena is that (1) persistent pain following a sprain is due to pressure exerted by edema fluid which has accumulated within the inextensible sheaths of ligamentous structures, and (2) that abolition of pain by local injection techniques is due to mechanical release of pressure when the needle ruptures these encapsulations which represent the trigger areas.

**The analgesic action of 1,1-diphenyl-1-(dimethylaminoisopropyl)-butanone-2 in man.** ERIC ANGLIN B. THOMAS (introduced by Raymond N. Bieler) *Dept of Pharmacology, Univ of Minnesota, Minneapolis*. The above named chemical, the pharmacology of which was presented by Scott and Chen a year ago, (Fed Proc 5:201, 1916) has been supplied to us for clinical trial by Dr. K. G. Kohlstaedt of The Lilly Laboratory for Clinical Research. It has been given the name of Dolophine. The compound has been studied on more than 300 patients, in a dosage range chiefly of 5-10 mg, in the University of Minnesota Hospitals. It has been administered orally and by parenteral injection for all types of pain. Wherever possible its effects have been compared to those produced by Morphine sulfate and Isomorphine HCl. In the entire series, 85% of patients obtained adequate to complete relief of pain and thought the drug was as good or better than morphine and isomorphine. Incidence of side effects was 15%. This included nausea and vomiting, euphoria, dry mouth, dizziness, miosis, pinpoint pupils, stupor, and respiratory depression.

As far as can be determined identical compounds have been supplied to us by Dr. George Hazel of the Abbott Laboratories (AN 118) and by Dr. J. C. Rice of the Winthrop Chemical Company (A 1621). In a limited number of comparisons, no differences between the three compounds have been observed. This is pointed out because the compound has in asymmetric C atom and therefore, the d, l, and racemic forms might possess different degrees of activity.

**Antagonism between curare and physostigmine.** KINGS R. LUNA and KAZUO K. KIKUCHI (by invitation) *Dept of Pharmacology, Univ of Illinois College of Medicine, Chicago 12*. The LD<sub>50</sub> of D-tubocurarine chloride (DTC), 0.77 mg/kg, s.c., in mice was increased to 1.5 mg/kg by premedication of the animals with either physostigmine (0.15 mg/kg, s.c.) or neostigmine (0.3 mg/kg, s.c.). Pretreatment of the mice with disodium propylthiophosphite (DFP), 3 mg/kg, i.p., failed to increase significantly the LD<sub>50</sub> of DTC.

On the other hand, treatment of mice with small nonparalyzing doses of DTC (0.25 mg/kg, s.c., given twice within 15 minutes) afforded a different degree of protection from the toxic effects of physostigmine and those of neostigmine. The LD<sub>50</sub> of physostigmine was increased 100%, whereas the increase was only 31% with neostigmine. Atropine, likewise, afforded a different degree of protection from the two drugs. The LD<sub>50</sub> of physostigmine in atropinized mice (10-20 mg/kg, s.c.) was increased eight fold while that of neostigmine was increased only 48%. The LD<sub>50</sub>

of DFP was not significantly increased by pre-treatment with atropine

The marked differences in the antagonistic effects of physostigmine, neostigmine, or DFP on DTC toxicity and, inversely, of curare on the toxic effects of physostigmine and neostigmine do not parallel the effects of these parasympathomimetics on their inactivation of cholinesterase. Hence, the results indicate that the mutual antagonism between curare and physostigmine or related drugs is independent of the action of acetylcholine at the myoneural junction

A preliminary report on the local anesthetic properties of various aromatic carboxylic acid esters. KARL F. URBACH, WILLIAM C. NORTH and JOSEPH L. GLASER (introduced by Carl A. Dragstedt) *Dept of Pharmacology, Northwestern Univ Medical School, Chicago, Illinois*. For the purpose of testing the hypothesis that extension of double bond conjugation increases activity of local anesthetics of the benzoic acid ester type, 4,4'-diethylaminoethyl stilbenedicarboxylate (I), 4,4'-dimethylaminoethyl stilbenedicarboxylate (II), 4,4'-diethylaminoethyl dibenzylidicarboxylate (III), and 4,4'-dimethylaminoethyl dibenzylidicarboxylate (IV) were synthesized (Fosdick and Urbach, *J Am Chem Soc*, in press). These compounds were tested for activity on the rabbit's cornea and by intradermal wheals in guinea pigs. Toxicities were determined by estimating the LD<sub>50</sub> after intraperitoneal injections into mice. The average results of the data obtained are indicated in the following table

Compound	LD <sub>50</sub> (mice I.P.)	Duration of anesthesia (G.P. wheel 1% sol'n)	Duration of anesthesia (rabbit cornea 1% sol'n)
Procaine	216 mg/kg	25 min	
Cocaine	72 mg/kg		41 min
I	237 mg/kg	30 min	40 min
II	457 mg/kg	18 min	32 min
III	420 mg/kg	31 min	31 min
IV	675 mg/kg	15 min	5 min

It is evident that the diethylaminoethyl esters (I, III) are more active, as well as more toxic, than the corresponding dimethylaminoethyl esters (II, IV). It would appear that the stilbene derivatives are more active than the dibenzyl derivatives when tested on the rabbits' cornea, but not on injection. However, from the data thus far obtained it is not possible to draw definite conclusions as to the influence of extension of double bond conjugation on local anesthetic activity. We are actively engaged in more detailed studies on these, as well as related compounds, and shall present further results.

Some observations on distribution and excretion of 1'-ethyl-3,6-dimethyl-2-phenyl-4-pyri-

mido-2'-cyanine chloride (CMR Center No 863) in dogs. ARTHUR D. VALA, JR. (by invitation), LAWRENCE PETERS and ARNOLD D. WELCH *Dept of Pharmacology, School of Medicine, Western Reserve Univ, Cleveland, Ohio*. A method for the determination of this drug in blood and tissues, with an error not exceeding 10%, has been devised. This was based on extraction with iso amyl alcohol, transfer to aqueous acid, partial neutralization, return to iso amyl alcohol, and spectrophotometric determination at 494 mμ.

The compound rapidly disappeared from blood after intravenous injection. Thus, intravenous administration of 5 mg/kg produced the following concentrations in the blood: 0.3, 0.12, and 0.02 mg per cent, at 2, 15, and 60 min, respectively. Urinary excretion rarely exceeded 5%. Ten to 15% of doses of 5 mg/kg, given during ½ hour by venoclysis, appeared in the bile. The materials recovered from urine and bile possessed absorption spectra and chromatographic properties significantly different from those of the injected material. Studies of the nature and antifilarial activity of these metabolic conversion products are in progress.

Essentially complete analysis of body tissues, total bile and total urine, indicated that the drug is rapidly degraded. About 90% was accounted for 30 min after administration, but only about 30% was recovered after 26 hours (excretion by the intestinal mucosa was not studied). The concentration of drug in the kidney was usually at least 10 times that of any other tissue, when dried from the frozen state, the drug was visible microscopically, predominantly in the convoluted tubules.

Although single doses of 5 mg/kg disappeared practically completely from the body in 72 hours, repeatedly daily intravenous administration of doses of 2 mg/kg resulted in some accumulation.

Effect of PABA as antagonist to organic bismuth preparations. ELBERT VOSS<sup>1</sup> (introduced by A. L. Tatum) *Dept of Pharmacology, Univ of Wisconsin Medical School, Madison*. p-Aminobenzoic acid, in addition to its effects on sulfonamide action and its beneficial action in the treatment of rickettsial diseases, has been demonstrated by Sandground and associates to be effective in counteracting the toxicity of a number of pentavalent arsenic compounds.

Since certain bismuth preparations have some similarities in common with arsenical drugs, it was thought that a study of PABA in acute intoxication might be of interest in extending the scope of coverage. Consequently a series of experiments were performed involving the concurrent actions of organic preparations of bismuth

<sup>1</sup> Present address—School of Pharmacy, Creighton University, Omaha, Nebraska.

and of PABA. It was found that PABA given intravenously to rats actually reduced the toxicity of such bismuth preparations as the tartrate, malonate and citrate when also administered intravenously. The efficiency of PABA is not nearly so dramatic for bismuth as it is for pentavalent arsenicals, yet it is sufficiently definite as to be beyond any reasonable doubt. The mechanism of action has not been determined and, furthermore, owing to the very moderate effects, it is not proposed as an effective antidote for acute bismuth poisoning.

**The action of alstonine.** K. G. WALKER and K. K. CHEN, *Indiana Univ. Medical Center, and the Lilly Research Labs., Indianapolis.* Experiments were carried out with the alkaloid alstonine hydrochloride to ascertain its action on experimental malaria, blood pressure, respiration, heart, smooth muscle organs, blood sugar, and urine. Its acute toxicity was also determined in mice and rats. Alstonine HCl has an antimalarial action against *Plasmodium lophurae* in ducklings, being approximately  $\frac{1}{3}$  as active as quinine dihydrochloride. The alkaloid, however, is much more toxic than quinine. Alstonine HCl lowers blood pressure of anesthetized dogs, cats, and rats, and reduces the pressor response of adrenalin in the same animals (adrenolytic action). In large doses, alstonine HCl has a deleterious effect on the heart, and in fatal doses, it causes primary respiratory failure in experimental animals. Alstonine HCl frequently inhibits the peristaltic movements of isolated intestines of rats, guinea pigs, and rabbits, contracts the isolated uterus of the guinea pig, and dilates the bronchioles of pithed dogs. The alkaloid is apparently excreted in urine.

**Pharmacologic characterization of an aliphatic amine, 2-methylamino-6-hydroxy-6-methyl heptane.** R. P. WALTON, M. BELKIN (by invitation) and O. J. BRODIE (by invitation), *Dept. of Pharmacology, Medical College of South Carolina.* Special cardiotoxic effects and a wide margin of safety have been reported recently for this aliphatic amine (EA 83) by D. E. Jackson (Curr. Res. Anes. Analg. in press). The report here essentially confirms and extends these findings. In open chest dog preparations, intravenous doses of 0.2 mg. produced distinct increases in myocardial contractile force lasting several minutes. (All doses on a per kg. basis calculated as the free base.) Larger single doses up to 80 mg. produced more marked and prolonged effects without significant depressor phases and without special incidence of rhythm irregularities. Pressor action was consistent but relatively moderate, heart rate usually increased about 20% in these vagotomized animals. Several successive doses in one instance totalling up to 700 mg. did not immediately terminate the experiment. With successive doses,

responses progressively but slowly diminished in intensity, reversal effects occurred only with relatively large doses. With intact, normal animals, the LD<sub>50</sub> was approximately 200 mg. (intravenously) for mice, rabbits and dogs. In mice, the LD<sub>50</sub> was 1500 mg. (subcutaneously) and 3000 mg. (orally). Apparently, prompt deaths were due to overstimulation of the respiratory center and late deaths secondary to pulmonary edema. Analeptic effects in dogs, local mydriatic effects in rabbits and stimulant effects on the isolated rabbit heart were negligible. No toxic effects were observed in dogs receiving 120 mg. daily in capsules and mice receiving 800 mgm. daily in drinking water for a period of 90 days. Local induration and occasional sloughing followed subcutaneous injections of the mucate in mice but did not follow injections of the hydrochloride or mucate in rabbits and dogs. Subcutaneous injections of 80 mg. in open chest dogs produced prolonged, intense and uniform augmentation of myocardial contractile force. After the heart had become refractory to such doses, digitalis produced its typical effects.

**Effect of drugs on myocardial contraction force as measured under conditions of an intact circulation.** R. P. WALTON and O. J. BRODIE (by invitation), *Dept. of Pharmacology, Medical College of South Carolina.* Isometric systolic tension in a section of myocardium was measured by means of a calibrated spring interposed in the lever system of the Cushing myocardiograph. The myocardiograph levers were attached in typical fashion to the anterior aspect of the right ventricle in an open-chest dog preparation. The tension of the spring at various lengths was calibrated in grams. In a representative experiment, the spring length necessary to dump the writing lever excursions to near extinction corresponded to a weight of 57 grams and this was taken to represent the isometric systolic tension (I.S.T.). Such figures were reasonably consistent during the control periods of  $\frac{1}{2}$  to 1 hour. Administration of digitalis (1 unit per kg.) raised the I.S.T. in 30 minutes to 104 grams and this higher level of tension, determined at intervals, was maintained with only a moderate decrease until shortly before fibrillation. Epinephrine in doses of 0.01 mg. per kg. usually caused a more marked increase in I.S.T. which lasted a few minutes and followed a parallel course to that of the blood pressure. Significant and characteristic increases in the I.S.T. were also obtained with ephedrin, caffeine, barium chloride, calcium chloride, potassium chloride and 2-methylamino-6-hydroxy-6-methyl heptane (EA 83). (This latter synthetic aliphatic amine has been reported recently by D. E. Jackson to have special cardiotoxic effects with little tachyphylaxis.) Results with quinidine and with amyl nitrite varied, according to conditions, from a slight increase to

ubstantial decrease in I S T Primary myocardial effects are considered to have a subordinate influence in results such as some of those obtained with potassium chloride, quinidine and amyl nitrite

Some factors affecting duration of action of local anesthetics when injected intracutaneously in guinea pigs NELLIE PERRY WATTS (introduced by Carl A Dragstedt) *Dept of Pharmacology, Abbott Research Labs, North Chicago, Illinois* In the screening of compounds for local anesthetic activity much information may be gained by their use in wheels It has for some time been the custom in this laboratory to use for this purpose guinea pigs previously depressed slightly by nembutal to rule out false responses to the hum of the inductorium, etc In addition, to make the test more critical control injections of procaine hydrochloride are given to each guinea pig Special studies have been made of some factors affecting the duration of procaine anesthesia and irritation Total volume of the injection, and the relation of the volume to the diameter of the wheel, concentration, frequency of stimulation, degree of hypnotic depression, age (size) of the guinea pig, location of the wheel on the body surface, etc These factors are correlated in setting up some standards which appear to give, under experimental conditions, less spread from average values

A cardiac action of tannins RUSSELL A WAUD and GWENDOLYN PEARSON KIRK (by invitation) *Dept of Pharmacology, Univ of Western Ontario, London, Canada* The tannins or tannic acid are substances of unknown and varying composition They are built up from relatively simple phenolic substances including gallic and pyrogallic acids Many of them are of a glucosidal nature

In the process of separation of cardiac active principles from certain plant extracts it was found that treatment with tannic acid increased the activity and its removal with a heavy metal had the opposite effect It was, therefore decided to investigate the action of tannic acid on the heart

Isolated hearts were perfused until they showed definite signs of fatigue Tannic acid in a concentration of 1:50,000 when added to the perfusion fluid produced augmentation which was maintained over a relatively long period Later the tonicity of the myocardium was increased and a high percentage of hearts finally stopped in systolic standstill

It was then decided to try and separate out the cardiac active principle A white or grayish white powder freely soluble in water but insoluble in dioxane was isolated This substance produced marked cardiac augmentation in a concentration of 1:500,000 while 1:5,000,000 produced the characteristic but not a maximum effects The characteristic effect was nearly always that of simple augmentation There was both increased relaxation

and height of contraction The effect upon the rate was little if any except that some hearts were slowed after long perfusion with the drug There was increased tone of the ventricle but systolic standstill was seldom attained

One way isonipeaine-trimethadione antagonism E LEONG WAI, SAMUEL S BINDER and ARNOLD H MICHAEL (introduced by Paul K Smith) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* The anticonvulsive effects of trimethadione (tridione) against isonipeaine (demerol) overdosage were investigated on white mice The intraperitoneal median lethal dose ( $LD_{50}$ ) of trimethadione over a forty eight hour period was found to be  $1930 \pm 68.9$  mg/kg (S.E.) One eighth to one-fifth the  $LD_{50}$  of trimethadione aborted convulsions totally or in part and prevented deaths in a significant number of animals given a lethal subcutaneous dose of isonipeaine (225 mg/kg) One-half the  $LD_{50}$  of trimethadione antagonized isonipeaine convulsions, but some animals died in respiratory depression It is concluded, therefore, that the relationship between isonipeaine and trimethadione is qualitatively similar to that previously determined by one of us on isonipeaine and the barbiturates (*J Pharmacol* 87:265-272, 1946), i.e antagonism acts only in one direction Although trimethadione protects animals from the lethal convulsive effects of isonipeaine, isonipeaine increases the depressive properties of trimethadione [Aided by a grant from the Winthrop Chemical Co.]

The tissue distribution of isonipeaine (demerol) E LEONG WAI, ABRAHAM I GRIMBLE and E WILLIAM LIGON, JR (introduced by Paul K Smith) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* The tissue distribution of isonipeaine (demerol) was investigated using a modification of Brodie and Udenfriend's methyl orange method (*J Biol Chem* 158:705-714, 1945) Four rats were each injected hourly with two 50 mg/kg doses of isonipeaine intraperitoneally and two hours after the second dose, the animals were sacrificed Highest concentrations of apparent isonipeaine were detected in the lungs, liver and kidney and extremely low levels were found in the blood Average concentration (mg/kg) found in each tissue with its respective mean deviation was lungs  $82.7 \pm 13.9$ , liver  $56.1 \pm 13.6$ , kidney  $51.8 \pm 10.2$ , spleen  $34.8 \pm 9.9$ , brain  $11.7 \pm 2.5$ , heart  $10.0 \pm 3.4$ , muscle  $9.1 \pm 2.4$ , blood  $3.3 \pm 0.2$ , urine  $828 \pm 126$  The total amount found in the urine was less than four per cent of the dose administered

With the exception of one individual who showed a blood level of about 1.25 mg/l in 30 minutes and 0.5 mg/l after two hours, isonipeaine could not be detected (sensitivity = 0.5

mg/l) in four humans after a 100 mg dose of isonippecaine intramuscularly. Also, no isonippecaine could be found in the milk of patients two to six hours after 100 mg intramuscularly. Appreciable apparent isonippecaine was found in the urine of three newborns three to nineteen hours after delivery [funded by a grant from the Winthrop Chemical Co.]

**The effects of isonippecaine (demerol) on auricular fibrillation** E LEONG WAY, ROBIN C GRUBBS and ROLAN SWANSON (introduced by Paul K Smith) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* Studies on the effects of isonippecaine (demerol) on experimental auricular fibrillation were made on dogs anesthetized with sodium barbital, 0.25 to 0.3 gram/kg, and maintained with artificial respiration. Fibrillation of the auricles was effected either by faradic stimulation or by the method of Nahum and Hoff (*Am J Physiol* 129:128, 1940), using rectyl betamethylcholinc chloride (mecholy). Electrocardiograms were taken during various stages of the experiments.

In four of five dogs it was found that isonippecaine, 2.5 to 5 mg/kg intravenously, raised the faradic threshold for the production of auricular fibrillation for a period of 10 to 25 minutes, the duration of action being proportional to the dose given.

Also, in five dogs with mecholy-induced "fibrillation," intravenous isonippecaine, 2.5 to 5 mg/kg, rendered the auricles less or non-responsive to a second application of mecholy for 15 to 40 minutes. It could not be conclusively determined that isonippecaine was effective in stopping fibrillation because the arrhythmia so induced rarely lasted longer than eight minutes and varied in its onset and character. However, the duration of mecholy fibrillation was never greater and sometimes was less after isonippecaine [funded by a grant from the Winthrop Chemical Company].

**Studies on the urinary excretion of  $\beta$ -dimethylaminoethylbenzhydryl ether hydrochloride (benadryl)** E LEONG WAY, JOHN R OVERMAN and DONALD L HOWIE (introduced by Paul K Smith) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* Studies on the urinary excretion of  $\beta$ -dimethylaminoethylbenzhydryl ether hydrochloride (benadryl) were made on five individuals using a modification of Brodie and Udenfriend's methyl orange method (*J Biol Chem* 158:705-714, 1945). After a single 50 mg dose, equivalent to 43.8 mg base, it was found that the amount of apparent benadryl appearing in the urine varied from 3 to 13 per cent, the peak excretion occurring in two to six hours. The ingestion of ammonium chloride (3 to 4 grams in 8 hours) hastened and increased

the excretion of benadryl about threefold, whereas, sodium bicarbonate (1 gram) may have slightly decreased its excretion. Preliminary results indicate that at least part of the material in the urine reacting with methyl orange is a breakdown product rather than true benadryl.

**The influence of the liver on the activity of isonippecaine (demerol) in vivo and in vitro** E LEONG WAY, ROLAN SWANSON and ANTHONY I GRUBBS (introduced by Paul K Smith) *Dept of Pharmacology, The George Washington Univ School of Medicine, Washington, D C* In normal rats the duration of sleep after sodium pentothal, 40 mg per kg intraperitoneally, was found to be  $19 \pm 1.5$  minutes (S.E.). In another series, the same dose of pentothal plus 20 mg/kg of isonippecaine produced sleep lasting  $37.1 \pm 3.4$  minutes. After partial hepatectomy and a forty-eight hour recovery period, the duration of hypnosis was found to be  $27.6 \pm 2.8$  minutes with pentothal alone, whereas, with pentothal plus isonippecaine four out of eleven rats died and the survivors slept  $91 \pm 15.1$  minutes. Inasmuch as the duration of pentothal-induced sleep was only slightly altered by hepatectomy, it is concluded that the increased effect of pentothal in the pentothal-isonippecaine operation was due mainly to the inability of the liver to metabolize isonippecaine. Section of myocardium was made and isonippecaine was added to the bath. The calibrated spring interposed in the bath was used for one of the Cushing myoelectrograph electrodes. Udenfriend's methyl orange method was used in the anterior aspect of the right ventricle. The tensiometer was found to be of various lengths was calibrated in but remained uncalibrated experiment, the sprigle, heart, blood, brain and the writing lever for of one dog was also found to responded to isonippecaine. [Supported by a grant from the Winthrop Chemical Co.]

**Studies on the relative antifilarial activity of a series of cyanine dyes against *Leishmaniasis*** ARNOLD D WELCH, LAWRENCE PETERS, ERNEST BULFING, ARTHUR D VALK, JR (by invitation), and ALVIN HIGASHI (by invitation) *Dept of Pharmacology, School of Medicine, Western Reserve Univ, Cleveland, Ohio* Routine testing of many compounds for chemotherapeutic properties against the filarid, *L. carinii*, in the cotton rat, disclosed that the cyanine dye, (1-amy-2,5-dimethyl-3-pyrrole) (1,6-dimethyl-2-quinoline dimethinecyanine chloride) consistently killed all worms when administered intraperitoneally every 8 hours for 18 doses (0.1 mg/kg per dose) or every 24 hours for 5 doses (0.2 mg/kg per dose). These dose levels are 1/10 to 1/15 of those maximally tolerated by a laboratory strain of the same animal species.

Subsequent studies of related compounds in-



cluded a curative assay, and manometric measurement of the inhibition of respiratory metabolism of the parasite. The latter is indicative of the intrinsic activity and all compounds devoid of inhibitory effect on oxygen consumption were also inactive *in vivo*. However, numerous compounds which possessed considerable activity *in vitro* showed little or no activity *in vivo*, this was attributed to variations in distribution, inactivation and excretion.

Activity has been found only with those compounds in which a quaternary nitrogen is joined to a tertiary nitrogen through a chain of carbon atoms of uneven number, with alternating single and double bonds, both nitrogen atoms are usually, but not necessarily, part of a heterocyclic ring. The resonating system thus constituted appears to interfere with a specific stage of filarial carbohydrate metabolism.

These screening tests, and other factors to be discussed, led to the selection, from a large group of compounds synthesized by Brooker, et al of the Eastman Kodak Research Laboratories, of 1' ethyl 3, 6 dimethyl-2 phenyl 4-pyrimido 2' cyanine chloride (C M R Center No 863) for further study.

The influence of atropine on the central effects of di-isopropyl fluorophosphate (DFP) in experimental animals. W. CLARKE WESCOE, (by invitation), RAY E. GREEN, (by invitation), BERNARD P. MCNAMARA (by invitation), and STEPHEN KROP. *Pharmacology Section, Medical Division, Edgewood Arsenal, Maryland*. Observations have been made on the central excitatory action of DFP. Clinical manifestations of central stimulation were observed in the intact rat, guinea pig, cat, dog, and monkey with intravenous doses varying from 0.5 to 4.0 mg/kg in the different species, the monkey appears to be the most sensitive. These manifestations were agitation, hyperexcitability, and tonic clonic convulsions.

In curarized animals, including the dog, or high spinal cats and rats receiving artificial respiration, heightened central activity was noted in the electroencephalogram as evidenced by increases in frequency and potential. With spinal animals, increase in reflex hyperexcitability of the spinal cord was also observed after DFP, in the cat this was manifested by dramatic accentuation of the tendon, scratch, and crossed-extension reflexes as well as the onset of spontaneous clonus in the hind limbs, in the rat it was manifested by increased reflex response elicited by lightly tapping over the vertebral column.

The clinical convulsions, as observed previously by others, have been controlled in some species by intravenous atropine in doses ranging from 10 to 10.0 mg/kg. In the electroencephalogram after similar doses of atropine, the waves were returned

to base line activity and in some cases almost completely abolished. The spinal animals after atropine showed a rapid decrease in spinal reflex excitability, the reflexes then being obtained only with difficulty.

These results indicate that DFP exerts a stimulating effect both on the brain and cord and that atropine blocks this action at both sites.

A comparison of the inotropic effect of cardiac glycosides on isolated mammalian heart muscle. WALLACE F. WHITE (by invitation), JULIUS BELFORD (by invitation) and WILLIAM T. SALTER. *Laboratory of Pharmacology and Toxicology, Yale University School of Medicine, New Haven, Connecticut*. Purified cardiac glycosides have been compared with Ouabain Reference Standard (approximately 11% water of hydration) in their ability to increase the contractibility of hypodynamic papillary muscles of the cat heart. Each drug was tested at two or more dose levels and compared with U.S.P. XI Ouabain on the same sample of heart muscle. The responses of all these drugs conformed satisfactorily to a semi logarithmic dosage response curve, when the amplitude of contraction was expressed as a per cent of maximal. Two methods of computation were employed: (1) The two by two or three-by-three method of Bliss was applied in the usual manner. (2) All data were reduced to a common nomogram in which the 80-percentile response of ouabain was set at  $\log 10 = 1.0$  on the log dose abscissa. Both methods checked satisfactorily. The following reciprocals of potencies, in terms of weight, were obtained: Cerberin 0.61, Convallotoxin 0.61, Scillarin A 0.79, anhydrous ouabain 0.89, Calotropin 0.90, Cyamarin 0.90, U.S.P. XI Reference Ouabain (11% water) 1.0, Oleandrin 1.3, Digitoxin 2.3, Cerberoside 3.9, Thevetin 6.6, Uzarin 36.5.

These data were obtained with only a few milligrams of each pure glycoside (supplied by K. K. Chen). It is interesting that these estimates compare rather well with those reported in the literature in toxicity studies on intact animals, but there are a few interchanges in the order of potency. [Work aided by grants from the Life Insurance Medical Research Fund and Navy contract N60r1 44, Task Order -VI.]

The percutaneous toxicity of thioglycolates. MARIE F. WHITESELL (by invitation), ELSIE ALVAREZ (by invitation) and JOHN H. DRAIZE. *Division of Pharmacology, Food and Drug Administration Federal Security Agency, Washington 25, D.C.* The cold "permanent wave" process consists, in part, in a redening action on the proteins of the hair. A 7 per cent thioglycolic acid solution adjusted to pH 9.0-9.5 (ordinarily with ammonia) is the common waving agent employed.

Salts of thioglycolic acid (sodium, calcium, ammonium, monoethanolamine and triethanol

amine) may be absorbed percutaneously by animals to produce systemic poisoning, but the dose level required is higher and the manner of application more rigorous than those specified in directions accompanying waving solutions intended for use by beauticians and in home applications.

Blood examinations in animals treated according to the method of Draize et al, *J Pharm & Expt Therap* 82:377, 1944, reveal minor fluctuations in hemoglobin levels and volume of red cells even at doses of 40 ml/kg/day. This latter dose level elicits a two to threefold increase in total urinary sulfur excretion. Ammonium dithiodiglycolate and ammonium thiodiglycolate (an oxidation product and a contaminant, respectively in common wave solutions) are less toxic than ammonium thioglycolate. Similarly, fractions representing various stages in the manufacture of ammonium thioglycolate are less toxic than the active waving ingredients.

These studies support the view that ammonium thioglycolate hair wave solutions are safe for use if the usual directions are carefully followed.

**Tolerance and Physical Dependence in Intact and chronic spinal dogs during addiction to 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3)** ABRAHAM WIKLER and KARL FRANK (by invitation) *Research Dept., U S Public Health Service Hospital, Lexington, Kentucky*. In intact dogs receiving subcutaneous injections of 10820 it mes daily increasing gradually from 1.0 to 5.0 mg/kg tolerance to the sedative, analgesic (tooth pain reaction threshold), and hypothermic effects of the smaller doses was evident at the end of the first week and to those of the largest dose at the end of the eighth week, when injections were discontinued abruptly. Twelve to 18 hours later, marked restlessness, tremors, muscle twitches, panting, pyrexia, mydriasis, rhinorrhea, occasional vomiting and mild diarrhea were observed. The abstinence syndrome reached a peak about the 24th hour and largely disappeared by the 48th hour. After one week tolerance was markedly reduced. The 10820 abstinence syndrome appeared to be more rapid in onset, more severe and of shorter duration than that of morphine in dogs.

In chronic spinal dogs similarly treated, partial tolerance to the effects of even 5 mg/kg of 10820 on the hindlimb reflexes was noted at the end of the 8th week. Following abrupt withdrawal, in addition to the abstinence syndrome above the level of spinal cord transection (lower thoracic), greatly exaggerated running movements of the hindlimbs appeared, reaching a peak at the 36th hour with gradual subsidence during the next two weeks. During this period the flexor reflex was hyperactive and the extensor thrust reduced. Afterward the reflexes returned to the approximate

preaddiction level. Artificially induced pyrexia failed to reproduce the hindlimb abstinence syndrome. The latter resembled strikingly the effects of eserine on the hindlimb reflexes and the changes in the latter during morphine withdrawal.

Effects of single doses of 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3) on the nervous system of dogs and cats. ABRAHAM WIKLER, KARL FRANK (by invitation) and ANNA J EISENMAN (by invitation) *Research Dept., U S Public Health Service Hospital, Lexington, Kentucky*. In intact dogs, subcutaneous injection of 2-10 mg/kg of 10820 caused sedation, elevation of tooth pain reaction threshold (facial twitch in response to bipolar electrical stimulation of tooth), hypothermia, bradycardia, salivation and slowing of cortical electrical activity. In conditioned reflex experiments the degree of impairment of adaptive response patterns varied inversely as their stability (predictability). Blood sugar was elevated about 30% by initial doses of 0.5 to 5.0 mg/kg. Doses of 50 mg/kg caused convulsions, usually with spontaneous recovery.

In chronic decorticated dogs 2-5 mg/kg caused whimpering, immobility, abolition of "sham rage" reactions to restraint or nociceptive stimulation, elevation of tooth pain reaction threshold, bradycardia and hypothermia.

In chronic spinal dogs (lower thoracic level) 2-5 mg/kg reduced or abolished the hindlimb flexor, crossed extensor and Philipson's reflexes, augmented the extensor thrust, and altered the amplitude of the knee jerk but little.

In chronic decorticate cats, 1-5 mg/kg caused elevation of threshold for nictitating membrane responses to nociceptive stimuli (electrical stimulation of skin through Michel clip electrodes), pyrexia, mydriasis, extensor rigidity of forelegs and delayed motor restlessness, instead of evoking "sham rage," nociceptive stimulation inhibited motor activity and augmented rigidity and opisthotonos.

In acutely decerebrated cats, effects of 2-5 mg/kg varied with the exact level of the preparation. Extensor rigidity was slightly augmented or diminished, respiratory rate generally slowed and, in one experiment, delayed running movements appeared which ceased during application of pressure to extremities or tail.

In general, in all preparations, 10820 acted like morphine.

Effects of naphuride sodium (suramin) on respiration and morphology of lymphoid tissues of rats. W. LANE WILLIAMS, FRED G. BRAZDA and MARGARET S. WIEDORN (introduced by R. N. Bieter) *Depts. of Anatomy and Biochemistry, Louisiana State Univ. School of Medicine and The Dept. of Anatomy, Univ. of Minnesota*. The present experiments are extensions of studies

which demonstrated that suramin damaged normal and neoplastic lymphoid tissues of mice. Twenty adult rats received daily subcutaneous injections of 4 or 5 mg (aqueous solution) of suramin per 100 grams body weight for 5 to 8 days. After 5 days of treatment the oxygen uptake of tissues from these and from untreated rats was determined by the Warburg technique. Spleens of treated rats showed a very slight increase in oxygen utilization (Qo<sub>2</sub>—controls 11.88, treated 12.64). Oxygen consumption of lymph nodes (mesenteric) was increased by about 50% (controls 4.47, treated 6.77). Respiration of renal and hepatic tissue was unaltered. Histologically, lymph nodes were the first tissues to demonstrate changes (depletion and necrosis of lymphocytes, engorgement of sinuses with erythrocytes). During this period animals appeared well and body weights were unchanged. The toxic effects of suramin seemed to be limited to damage of lymph nodes, the above described increases in oxygen utilization of lymphoid tissue and prolonged bleeding and clotting times.

Terminally (after 8 days of treatment) suramin caused widespread hemorrhagic lesions and severe anemia (av rbc 2.4 million, Hgb 5.3 gram). There was hematuria and kidneys showed damage which included swelling and necrosis of tubular epithelium and hemorrhages. The previously mentioned changes in the lymph nodes were more extensive.

**Renal effects of uranium.** J. H. WILLS and E. MARY (introduced by Raymond N. Bieter) *Division of Pharmacology and Toxicology, Dept of Radiology, School of Medicine and Dentistry, Univ of Rochester, Rochester, N. Y.* Hexavalent uranium injected intravenously into rabbits was excreted in urine more rapidly than was tetravalent, and was fixed in the kidney to a greater extent. Bicarbonate more than either citrate or lactate decreased renal fixation of hexavalent uranium; tetravalent uranium was complexed slightly more by citrate than by bicarbonate. For hexavalent uranium the ratio of the sum of renal tubular fixation and excretion to glomerular filtration averaged 105%.

Rabbits and dogs injected intravenously with uranyl salts or exposed intermittently to uraniferous atmospheres showed decreases (within 2-5 days) in the renal clearances of chloride, creatinine, diodrast, inulin, phenol red, and urea. Secretion (diodrast and phenol red) was affected more than either reabsorption (chloride and urea) or filtration (creatinine and inulin).

About two hours after intravenous injection of uranyl salt, there were significant changes in the clearances of glucose and diodrast, those of amino acids, chlorides, creatinine, inulin, phenol red, urea, and xylene were not affected significantly.

These findings indicate that uranium probably has no direct effect upon the glomerulus and that its tubular action is confined to the latter part of the proximal convoluted tubule, where the metal probably is fixed to the epithelium. They support also the conclusion (Bobby, M. E. et al., *Am J Physiol* 139:155, 1943) that the essential change produced by uranium is alteration of the physical and chemical properties of the tubular epithelium rather than interference with the glomerulus.

**The toxicity and pharmacology of rutin.** ROBERT H. WILSON, TALBOT G. MORTAROTTI (by invitation) and FLOYD DEEDS *From the Pharmacology Division, Bureau of Agricultural and Industrial Chemistry, U. S. Dept of Agriculture, Albany, California.* Rutin, a rhamnoglucoside of the flavonol quercetin, is being used therapeutically in conditions characterized by an abnormal capillary permeability or fragility. No toxic symptoms following the therapeutic use of rutin have been reported, and we have found no evidence of acute or chronic toxicity in experimental animals. The maximum doses in acute experiments were 40 mg/kg intraperitoneally and intravenously in guinea pigs, 50 mg/kg intraperitoneally in rats, and 100 mg/lg intravenously in rabbits. Continued feeding to rats of a diet containing 1% rutin for 400 days produced no evidence of chronic toxicity.

When segments of guinea pig colon were suspended in 50 ml of aerated Ringer Locke solution, the addition of 0.2 mg of rutin had no effect per se, but always prolonged the action of epinephrine as reported previously. However, we found that 0.5 mg or more of rutin relaxed such intestinal strips occasionally, the frequency of relaxation increasing with the dose of rutin. These same effects were more pronounced when the aglycone, quercetin, was used. Both rutin (0.25 mg/ml) and quercetin (0.02 mg/ml) increased the amplitude of the beat of the Straub heart preparation, as reported previously. We found, in addition, that prolonged contact of the isolated heart with these agents, or the application of higher concentrations, depressed the heart muscle after brief stimulation.

The intravenous injection of 0.25 mg/kg of histamine killed 58% of 25 guinea pigs. When this dose of histamine was preceded by the intraperitoneal injection of 10 mg of rutin 10-30 minutes earlier, 15 out of 17 guinea pigs survived.

**Further studies on d-lysergic acid, d,l hydroxybutylamide 2 (methergine).** W. M. WILSON (by invitation), A. C. KIRCHHOFF (by invitation) and N. DAVID *Dept of Pharmacology, Univ of Oregon Medical School, Portland, Oregon.* We previously reported on a clinical trial of d-lysergic acid, d,l hydroxybutylamide 2 (Methergine), a synthetic ergonovine like compound, in 26 pa-

tients (Western Journal Surg, Obs and Gyn 52 197 (May) 1944) Since then an additional 75 patients have been given the drug intravenously and 9 patients intramuscularly immediately after delivery Methergine caused prompt, vigorous uterine contractions No untoward side effects were noted Blood loss was decreased from normal Results were felt to be equal to or superior to Ergonovine

**The relation of blood nicotine levels to type of smoking** WILLIAM A WOLFF and MARIA A HAWKINS (introduced by Harold D Green) *Tobacco Research Lab, Bowman Gray School of Medicine, Winston Salem, N C* A relationship has been demonstrated between the level of blood nicotine and the amount of cigarette smoke inhaled over a given time A series of preliminary experiments was made on twenty males, ages 20 to 30 years, all habitual smokers consuming 20 or more cigarettes per day Each subject abstained from coffee and other purine containing beverages for a period of 48 hours and from smoking for 8 hours prior to the experiment In each experiment, the subject smoked 5 to 8 cigarettes during the first hour and 15 or more during the next 7 hours Blood samples were drawn before smoking, after one hour, and after 8 hours The nicotine content of each sample was determined by the authors' method (Wolff and Hawkins, in press)

In general, the blood level of nicotine paralleled the amount of smoke inhaled In 3 subjects, the first blood sample was free from nicotine, the highest level after smoking was 1.32 mg/L The group inhaling little or no smoke averaged 0.05, 0.10, and 0.09 mg nicotine per liter, respectively, for the initial, one hour, and eight hour samples of blood, the group inhaling a moderate amount of smoke showed an average of 0.26, 0.32, and 0.28 mg/L, respectively, the group of deep inhalers averaged 0.27, 0.48, and 0.62 mg/L, respectively If data are recalculated to show the maximum rise in blood nicotine for each subject, the slight, moderate, and deep inhalers show group average increases of 0.07, 0.15, and 0.45 mg/L, respectively

**Influence of cardiac glycosides on respiration and glycolysis of heart muscle and brain cortex** ALBERT WOLLENBERGER (introduced by Otto Krayer) *Dept of Pharmacology, Harvard Medical School* The oxygen uptake of slices of guinea pig heart muscle, in the presence of glucose or lactate, is increased by ouabain in concentrations ranging from  $2$  to  $3 \times 10^{-7}$  M ( $1$  to  $1,500,000$ ), at higher concentrations, this increase (maximally 50%) is followed by a depression (maximally 80%) Of other guinea pig tissues studied, brain cortex alone responds similarly, but is only  $\frac{1}{2}$  as sensitive as cardiac muscle Digoxin and k-strophanthin produce the same effects

is ouabain, the former being 2-3 times, the latter about  $\frac{1}{2}$  as potent

Anaerobic glycolysis is moderately depressed by ouabain without preceding stimulation Succinate oxidation in heart muscle slices is not inhibited at all In brain, the increase in respiration is accompanied by the appearance of strong anaerobic glycolysis, which with the onset of respiratory depression reaches the level of the inhibited anaerobic glycolysis

Ouabain has no effect on the respiratory activity of homogenized heart and brain and of isolated oxidative enzyme systems Its stimulating action on the respiration of the intact tissues is dependent upon the presence of substrate in the surrounding Its inhibitory action is not reversed, but intensified by washing On the other hand, full protection against inhibition of both aerobic and anaerobic metabolism is afforded by adding boiled extract of heart muscle to the suspension medium

These findings suggest that the increase in metabolic activity produced by the cardiac glycosides is due, at least partly, to greater availability of exogenous substrate, and the inhibition to loss of one or more diffusible, heat stable oxidative catalysts

**Toxicological studies on the isomers and mixtures of isomers of benzene hexachloride** GEORGE WOODWARD and LESTER C HIGAN (introduced by Arnold J Lehman) *Division of Pharmacology, Food and Drug Administration Federal Security Agency, Washington, D C* The marked differences in biological activity observed between stereoisomers is well illustrated by the isomers of benzene hexachloride By either oral or intravenous administration in both mice and rabbits the order of decreasing activity is gamma, alpha, delta, beta The acute oral LD 50's in mg/kg for the gamma isomer are: For mice 86, for rats 177, for guinea pigs 127, and for rabbits 60 The other isomers are from  $\frac{1}{2}$  to  $\frac{1}{3}$  as toxic

The gamma isomer is a central nervous system stimulant with a relatively short duration of action The alpha and the delta isomers are central nervous system depressants with a longer duration of action Animals poisoned with the delta isomer also exhibit a low grade catalepsy

Mixtures of equal parts of alpha and gamma isomers and of delta and gamma isomers are more toxic than would be expected from their individual LD 50's

Two of three dogs receiving oral doses of 10 mg/kg of the gamma isomer daily except Sunday tolerated this dose for 18 and 49 days Three dogs similarly treated with 50 mg/kg of a technical benzene hexachloride containing 15.3% gamma isomer tolerated the material for 36, 46, and 49 days Some liver damage was noted in these animals

The influence of estrogenic substances upon the irritability of the uterine musculature and upon the cardiovascular system R A WOODBURY, DAVID MARSH,<sup>1</sup> RAYMOND P AHLQUIST and BERTHA HOBENSACK (by invitation) *Dept of Pharmacology, Univ of Georgia School of Medicine, Augusta, Georgia* Stilbestrol and estradiol increase the irritability of uterine muscular tissue of rabbits to acetylcholine, epinephrine, pitressin, pitocin, histamine, and stretch

In cats, dogs, rabbits, and humans, large doses of stilbestrol daily for 1 to 4 days, modifies the response of the cardiovascular system to acetylcholine, epinephrine, histamine, pitocin, and pitressin Blood pressure tracings from non-anesthetized animals and patients supplied the pre stilbestrolized response to measured doses of these drugs Repeating the observations after administrations of stilbestrol to the same animal or individual showed that the sensitivity to these substances was generally increased by two to ten fold, and a hundred fold increase was observed in some animals In a few animals the type of response was changed The relationship of these observations to menstruation, dysmenorrhea, pregnancy, and toxemia of pregnancy will be discussed [These studies were supported by financial grants from Eli Lilly and Company and Ciba Pharmaceutical Company]

The cardiovascular effects of sodium pentothal and sodium 5-allyl-5-(1-Methylbutyl)-2-thiobarbiturate in the dog L A WOODS (by invitation), J B WYNGAARDEN (by invitation), BARBARA RENNICK (by invitation) and M H SEEVERS *Dept of Pharmacology, Univ of Michigan* Sodium pentothal (I) and sodium 5 allyl 5-(1-methylbutyl) 2 thiobarbiturate (II) were compared on the dog heart lung preparation, using the rise in venous pressure and the decrease in cardiac output as indices of cardiac failure Whereas the ratio for anesthetic potency and lethality (respiratory failure) of I and II is approximately 1:1.5, the ratio for cardiotoxicity in these experiments is 1 < 1

The two compounds were also compared in dogs respiring spontaneously, and in others respiring artificially with positive intratracheal insufflation Each drug was administered intravenously either by intermittent injection at fixed intervals or by infusion at a constant rate An average of 1.5 times as much I as II (see above) is required to induce respiratory failure in dogs respiring spontaneously At identical infusion rates, artificial respiration permits the dog to survive a quantity of each drug which is 2.5 times the respiratory lethal dose Pulsus bigeminus and other arrhyth-

mias were invariably observed in the electrocardiogram during deep anesthesia accompanied by marked respiratory depression These arrhythmias were rarely observed in dogs under artificial respiration, and then only as a terminal event paralleling peripheral vascular failure

These experiments indicate clearly that respiratory failure is the primary cause of death from these thiobarbiturates in the intact dog Disturbances of rhythm and peripheral vascular failure observed in dogs in deep anesthesia are anoxic and reflex in origin and secondary to the failure of respiration, and are not due primarily to a direct toxic action of these compounds on the heart or peripheral vascular tree [Supported by a grant from Parke, Davis and Company]

The addiction potentialities of 1,1,-diphenyl-1-(dimethylaminoisopropyl)-butanone-2 (amidone) in the monkey L A WOODS (by invitation), J B WYNGAARDEN (by invitation), and M H SEEVERS *Dept of Pharmacology, Univ of Michigan* One group of rhesus monkeys received morphine sulfate subcutaneously daily for 86 to 95 days, increased from 7.5 to 100 mg/kg in 50 days and maintained at this level A second group received amidone subcutaneously for 75 to 96 days, the initial dose of 5 mg/kg being increased to a maximum of 12 mg/kg in the most resistant animals Anorexia and weight loss varying from 7-19% were noted equally in both groups Considerable irritation and fibrosis occurred at the site of injection with amidone, resulting in marked aversion to daily injections

The chronically morphinized monkeys exhibited characteristic abstinence signs (J Pharm & Exp Ther 56 147, 1936) on withdrawal Withdrawal from amidone was associated with return to normal activity, but no characteristic abstinence phenomena were detected

Acute depression from amidone, administered subcutaneously, reaches a maximum in 90 minutes and lasts 4-5 hours, as an average response Mydriasis, salivation, lacrimation, profound muscular weakness, and severe respiratory depression are characteristic signs, as with morphine The lethal dose lies between 10 and 20 mg/kg, death resulting from respiratory failure Repeated administration does not confer tolerance to the lethal dose nor to other manifestations of depression On the contrary, increased susceptibility is indicated, since profound depression demanded reduction in dosage below that previously tolerated Some crossed tolerance from morphine to amidone occurred, but monkeys chronically poisoned with amidone did not appear to have developed a crossed tolerance to morphine [Supported by a grant from Parke, Davis and Company]

Pharmacology of 1,1'-di-B-ethoxyethyl-2,2' carbocyanine P-toluene sulfonate and derivatives

<sup>1</sup> University of West Virginia Morgantown

in cotton rat filariasis HAROLD N WRIGHT, ASHTON C CUCKLER (by invitation) ELIZABETH M CRANSTON and RAYMOND N BIETER *Dept of Pharmacology, Univ of Minnesota Medical School, Minneapolis, Minnesota* Slight chemotherapeutic activity was encountered in diquinoxines of the type of 1,1' dimethyl 2,2' cyanine chloride in the treatment of *Lutomosoides carinii* infestations in the cotton rat. Somewhat greater activity was encountered when there were three carbon atoms in the linking chain as in 1,1' dimethyl 2,2' carbocyanine chloride. A very marked enhancement of chemotherapeutic activity was found, however, in 1,1' di-*n*-ethoxyethyl 2,2'-carbocyanine chloride and the corresponding p-toluene sulfonate derivative.

Administered intraperitoneally at eight hour intervals for 18 doses 1,1'-di-*n*-ethoxyethyl 2,2'-carbocyanine chloride was completely curative in (single) doses of 0.0167 mg/kg and had a therapeutic index (MTD/MCD) of at least 80, while the p-toluene sulfonate derivative was curative in the same dose, with a therapeutic index of 100. Both compounds are also highly active when administered intraperitoneally once daily for six days and because of the lessened toxicity at the less frequent rate of administration have therapeutic indices of 150-200 under these conditions.

The p-toluene sulfonate derivative has an intravenous acute LD<sub>50</sub> between 4.5 and 5.5 mg/kg for rabbits, guinea pigs and rats. Anesthetized dogs administered 1 mg/kg intravenously until death required doses of 8-26 mg/kg (mean 12.3). Dogs receiving 1 mg/kg doses of the compound intravenously twice or three times weekly have survived 50-80 injections without gross evidences of toxicity. Dogs receiving similar doses six times weekly have usually died after about 20 doses.

The work was done under contract with the Office of Scientific Research and Development, the Office of the Surgeon General of the U S Army, and the United States Public Health Service and the University of Minnesota. [Grateful appreciation is accorded to The Eastman Kodak Company and Parke, Davis and Company for supplying the compounds through the Chemotherapy Center.]

**Anesthetic properties of several thiobarbiturates in dogs** J B WYNGAARDEN (by invitation), L A WOODS (by invitation), R RIDLEY (by invitation), and M H SEEVERS *Dept of Pharmacology, Univ of Michigan*. Several thiobarbiturates, sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate (II), sodium 5-ethyl-5-isoamyl-2-thiobarbiturate (III), and sodium 5-isopropyl-5-(1-methyl-3-ethylallyl)-2-thiobarbiturate (IV) were compared with sodium pentothal (I) as to depth and duration of anesthesia after intravenous

administration in dogs. Data are presented in the table.

Drug	Dose (mg/kg acid wt.)	No. dogs	Duration of anesthesia av. in min. <sup>a</sup>
I	1.0	8	28
I	2.0 <sup>b</sup>	22	75
II	10.0	8	27
II	2.0	24	132
III	25.0	5	15
III	50.0	5	94
IV	12.5	8	59

<sup>a</sup> From onset of anesthesia to ability of animal to stand.

<sup>b</sup> Artificial respiration was necessary with a few animals to carry over initial period of apnea.

The approximate ratio of potency of these four compounds is I-1, II-1.5, III-0.5, and IV->1.5. Signs of induction, anesthesia, and emergence with II are comparable to I at a dosage ratio of 1:1.5. When these two drugs are compared at the same dose (25 mg/kg) II has an average duration of action 1.7 times that of I.

Effective anesthesia with compound III is characterized by slow recovery, due presumably to an inadequate rate of detoxication (see accompanying abstract).

Compound IV produces undesirable signs of stimulation [Supported by a grant from Parke, Davis and Company].

The cumulative action of certain thiobarbiturates in dogs J B WYNGAARDEN (by invitation), L A WOODS (by invitation), and M H SEEVERS *Dept of Pharmacology, Univ of Michigan*. In order to determine the approximate relationship which exists between duration of anesthesia and rate of detoxication several thiobarbiturates, sodium pentothal (I), sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate (II) and sodium 5-ethyl-5-isoamyl-2-thiobarbiturate (III), were administered intravenously in small dosage at hourly intervals, the volume of solution and rate of injection being constant. The dosage of each drug was selected on the basis of relative toxicity, anesthetic effectiveness and to produce anesthesia of short duration. The results obtained are tabulated below.

Drug	Dose (mg/kg acid wt.)	No. dogs	Duration of anesthesia (av. in min.) ± S.E.				
			0 hour	1 hour	2 hours	3 hours	4 hours
I	7.5	12	7.6 ± 2.20	14.8 ± 3.98	31.5 ± 6.57	78.0 ± 16.20	
II	5.0	16	5.5 ± 3.17	6.5 ± 2.16	11.3 ± 2.99	22.5 ± 7.50	41.5 ± 18.5
III	12.5	5	2.4 ± 0.48	8.4 ± 2.41	28.8 ± 9.07	67.4 ± 19.4	

Statistical differences in duration of anesthesia between these three drugs are not significant (95%) until the fourth injection (3 hours, table).

Since in the dosage ratio required to induce comparable initial duration of anesthesia II accumulates more slowly than I or III, it appears that a

lesser saturation of detoxication mechanisms occurs which may be of practical value [Supported by a grant from Parke, Davis and Company]

## THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

### THIRTY-SECOND ANNUAL MEETING

Chicago, Ill., May 18, 19, 20, 21, 22, 1947

(For possible corrections in any of the following abstracts see the next issue)

Continuous blood O saturation under pentothal-N<sub>2</sub>O-O anesthesia in clinical and experimental subjects VIVIAN G. BEHRMANN (by invitation) and FRANK W. HARTMAN Dept of Labys, Henry Ford Hospital, Detroit, Michigan. The extensive use in anesthesia of the combination of Pentothal and N<sub>2</sub>O O, each of which is capable of producing anoxia, formed the basis for this study of the blood O. Data on experimental and clinical subjects, accumulated through the use of a photoelectric method for the continuous recording of blood O saturation is presented.

Blood oximetry was followed under Pentothal anesthesia, supplemented by N O O mixtures, in proportions ranging from (25-75) to (80-20). Blood O saturation curves, coincident with tracings of mean blood pressure, pulmonary ventilation, costal and abdominal respiration were obtained on dogs under light, moderate, and deep anesthesia. The O saturation curves were calibrated using Van Slyke's method on arterial blood. The N O O mixtures were determined by the Van Slyke and Sendroy method.

Operations requiring  $\frac{1}{2}$  to 4 hrs of anesthesia were studied. The blood O curves on the clinical subjects included a normal (room air) record, the effect of the induction by intravenous Pentothal and any fluctuations occurring throughout the duration of the anesthesia. Although a 50:50 N O O mixture was preferred, the effects of altering the ratio of N O to O on the blood O curve were obtained. The marked variation in the sensitivity of individuals to Pentothal was often demonstrated. Under prolonged Pentothal anesthesia, high O administration did not always assure a safe blood O saturation level. For maximum safety, N O O mixtures should contain at least 40% O when used to supplement Pentothal anesthesia.

Phospholipids in thoracic duct lymph of rats. JESSE L. BOLLMAN, EUNICE V. FLOCK, JOHN H. GRINDLAY, and JAMES T. CAIR (by invitation). The Mayo Foundation, Rochester, Minnesota. Lymph from the thoracic duct of rats was collected through flexible plastic tubing inserted in the region of the cisterna chyli. The rate of flow in fasting rats was less than

1 ml each hour but often exceeded this volume following a meal or parenteral administration of fluid.

The amount of phospholipid in the lymph was usually higher than in the plasma of fasting rats. In rats fasted from 24 to 72 hours there was considerable variation in the phospholipid content of the lymph but the variations were not correlated with the time of fasting. After a meal containing neutral fat the concentration of phospholipid in the lymph rose to three or four times that of the plasma.

Radioactive phosphorus was injected into rats on the second day of lymph collection two hours after a meal containing neutral fat had been given by stomach tube. Lymph collections were continued for four hours and then the rats were anesthetized and blood, the liver, and the mucosa of the small intestine removed for analysis. The specific activity of the phospholipids of the liver was higher than that of the intestinal mucosa or that of the plasma and the specific activity of the lymph was considerably less since it represented an average over the time of collection of the lymph. This average usually approximated the average specific activity of the plasma for the same time period and was considerably less than that of the liver. Since the lymph collected was a mixture of systemic, intestinal and liver lymph, the source of the new phospholipid of the lymph could not be determined.

Clotting defect in hemophilia: deficiency in a plasma factor required for thromboplastin liberation from platelets. K. M. BRINKHOUS, Depts of Pathology, State Univ of Iowa and Univ of North Carolina. Previous experiments reported to this Society indicated that platelets or formed elements in hemophilic blood release their thromboplastin slowly, causing a delay in conversion of prothrombin into thrombin. In this paper data are presented which would indicate that a plasma factor is involved in the release of thromboplastin from platelets, and that this factor is deficient in hemophilia. Normal citrated plasmas which clotted slowly after recalcification were specially prepared by prolonged centrifugation of blood at 2°C in silicone treated glassware. These specially pre-



pared normal plasmas were much less effective than regularly collected normal plasmas in correcting the delayed clotting of platelet-free hemophilic plasma, and the normal plasmas with clotting times of 24 hours or longer were completely ineffective. However, such plasmas retained their corrective effect on the clotting of whole hemophilic blood. Also, after the addition of washed platelet suspensions, either normal or hemophilic, such plasmas corrected the clotting defect of platelet-free hemophilic plasmas. The platelet suspensions alone failed to reduce the clotting time of hemophilic plasma to normal.

**The influence of time of ingestion of essential amino acids upon utilization in tissue-synthesis.** P. R. CANNON, C. H. STIFFE (by invitation), L. J. FRAZIER (by invitation), D. A. ROWLEY (by invitation), and R. C. STIMRO (by invitation). *Dept. of Pathology, The Univ. of Chicago.* Adult male albino rats made protein deficient by dietary depletion recover lost weight steadily when fed a repletion ration which is adequate in calories, vitamins and minerals but contains, as the principal source of dietary nitrogen, only ten essential amino acids. If, however, the basal ration is divided into two portions, to one of which is added arginine, histidine, leucine, lysine and threonine, and to the other, isoleucine, methionine, phenylalanine, tryptophane and valine, and these two incomplete rations are fed alternately, poor weight-recovery ensues. This happens even when the rations are offered at alternate hours over a 14-hour period followed by the non-protein basal ration for the balance of the 24-hour period. Under these conditions the depleted rats, although ingesting adequate amounts of calories, vitamins and minerals, continue to lose weight. When, on the other hand, the two incomplete rations are combined and fed under similar alternating conditions, the animals eat well and recover weight rapidly. Moreover, when the depleted rats are offered free-choice of the two incomplete rations, in comparison with the combined ration, they still lose weight, due, presumably, to the fact that they do not eat the first ration in close enough relation in time to the second to effect complementation of the two groups of essential amino acids. These experiments suggest, therefore, that for effective tissue-synthesis all essential amino acids must be available in the tissues practically simultaneously, otherwise the first group absorbed is not stored long enough to enable its essential amino acids to combine with those of the second group for the synthesis of complete tissue-proteins.

**The different susceptibilities to nitrogen mustard of normal and malignant tissues growing in vitro.** IVOR CORNMAN and RICHARD A. ORMSBEE (introduced by Cornelius P. Rhoads). *The Sloan Kettering Inst. for Cancer Research,*

*New York, N. Y.* Observable responses in roller tube cultures to 24-hour dosage with *tris* (B. chloroethyl) amine are qualitatively the same in normal and malignant tissues, but may occur at different dosage levels.

Fibroblasts grown from fetal mouse subcutaneous tissue show increased granularity, opacity, shrivelling, rounding, and final disintegration at concentrations approximating 0.17 mM. Concentrations of 0.04–0.08 mM induce transient granularity and distortion of cell outline. Mitotic activity declines sharply and fibroblasts grow to abnormal size when returned to normal medium. Sarcoma 180 cells show same initial changes at 0.008–0.01 mM concentrations and moreover fail to grow when inoculated into susceptible mice. Killing *in vitro* requires 0.04–0.08 mM concentrations. Other sarcomas appear less sensitive.

Fetal mouse epidermal cells, like fibroblasts, are first affected at 0.04–0.08 mM and are killed by a 0.17 mM concentration. Increased granularity, opacity, and vesiculation of cell membrane are transient at the lower dose, permanent at the higher.

MA 387 (lung carcinoma) undergoes similar cytological changes at 0.08–0.17 mM concentrations and subsequently fails to grow in susceptible animals. These cells die at 0.10–0.33 mM concentrations. Mammary carcinomas EO 60 and 1025 are sensitive in same range as is normal epithelium, e.g. 0.04–0.08 mM.

Chick heart and frontal bone are the most resistant of tissues tested. The proliferating cells are damaged at 0.04–0.08 mM, die at 0.33 mM. Non-proliferating heart muscle cells continue to contract for one day at 0.65 mM and for 5 days at 0.33 mM.

**Mechanisms of aminoaciduria.** C. E. DENT (introduced by F. S. Robscheit-Robbins). *Medical Unit, Univ. College Hospital, London, and Dept. of Pathology, Univ. of Rochester, New York.*

The table summarizes two distinct mechanisms by which aminoaciduria, i.e. the excessive excretion of amino acids in the urine, can occur. The "Overflow" form is found in acute yellow atrophy of the liver and involves a simple spilling into the urine of the amino acids which are present in the blood in abnormally large amounts. The "Renal" form is found in Fanconi syndrome. In this disease a similar extent of aminoaciduria may occur although the blood level of amino nitrogen is normal. Examination of the urines by "Paper Partition Chromatography,"<sup>1,2</sup> discloses a further difference. In the "Overflow" form the urine contains large quantities of abnormal peptides as a sign of the gross derangement of amino acid

<sup>1</sup> Consden R., Gordon, A. H. and Martin A. J. P., *Biochem. J.* 38: 224 (1944).

<sup>2</sup> Dent, C. E., *Lancet*, November 2nd, 1946, p. 637.

metabolism which follows almost complete destruction of the liver. In the "Renal" form only one peptide, probably seryl glycyl glycine, is found. This is present in traces in normal urine. Other evidence is also against the possibility of an error of amino acid metabolism being present. In the Fenconi syndrome there are also functional and histological signs of kidney damage involving the mechanisms of tubular reabsorption.

	Normal	' Overflow aminoacid uria	"Renal aminoacid uria"
Blood NH <sub>2</sub> -N (mg/100 ml)	4-7	20-200	4-7
Urine NH <sub>2</sub> -N (mg/100 ml)	10-30	100-200	40-120
Urine (NH <sub>2</sub> -N/Total N) × 100	1-2	8-16	4-12
Peptides in urine	traces of one	many	large amounts of one
Duration		acute	chronic
Liver damage		always	sometimes
Kidney damage		sometimes	always

**Observations on normal and neoplastic mast cells in inbred strains and hybrid mice.** THELMA B. DUNN and MARGARET K. DERINGER (by invitation) *National Cancer Inst., Bethesda 14, Maryland*. Single longitudinal sections of spleens from several different inbred strains of mice were specially stained for mast cells, and the cells were counted. It was found that the number of mast cells in a single cross section appeared to be a strain characteristic. In strain A mice a number above 2,000 was frequently estimated in old males, while in strain I mice less than 5 of these cells were found in single sections. In fetal spleens from these two strains the number of mast cells appeared nearly equal.

Five cases of what appears to be neoplasia of mast cells have been observed. These were found in reciprocal F<sub>1</sub> hybrid mice of strains A and L. The abnormal mast cell accumulations were seen in the spleen, the lung, the kidneys, the duodenum and a lymph node. Previous reports of only three similar cases in mice have been found.

**The role of the salivary glands in the alarm reaction of Selye.** WILLIAM E. EHRLICH and JOSEPH SEIFTER (by invitation) *The Philadelphia General Hospital and The Wyeth Inst. of Applied Biochemistry, Philadelphia, Pa.* While studying the alarm reaction of Selye in rats injected with colchicin, selenium compounds and other drugs, it was noted that the organs affected included particularly those that had been reported to contain a great deal of ribose nucleic acid. When extending this study to the salivary glands which also contain abundant ribose nucleic acid, it was found that these glands too participated in the

alarm reaction. Microscopic examination revealed considerable degeneration and necrosis of the parenchyma of these glands and in many instances suppurative inflammation as well. These observations seem to throw light on the etiology of postoperative parotitis which so long defied explanation. It is suggested that this postoperative complication is another part phenomenon of the alarm reaction of Selye.

**Quantitative histologic study of the effect of chronic whole-body gamma irradiation on mouse testes.** ALLEN B. ESCHENBRENNER, EGON LORENZ, ELIZA MILLER (by invitation) *National Cancer Inst. and National Argonne Lab., Chicago*. Male mice were exposed to whole body gamma radiation at rates of 8 Sr, 4 4r, and 1 1r given in 8 hours per day beginning at 2 months of age. Four mice on each exposure level and nonirradiated mice of the same age were killed at intervals of 2 months after 2 to 16 months' irradiation. Data include fresh testes weights and quantitative histologic analysis of the interstitial and spermatogenic tissue by means of Chalkley's method. There was an initial decrease of testes weights after 4 months' irradiation after which they remained approximately the same, being 20% of normal in the 8 Sr mice, 60% of normal in the 4 4r mice, and 90% of normal in the 1 1r mice. After 16 months of irradiation the interstitial tissue comprised 27% of the entire testes in the 8 Sr mice, 12% in the 4 4r mice, and 6% in the 1 1r and nonirradiated mice. Multiplication of these per cent values by testes weights gave comparable figures for all mice, indicating that the apparent increase of interstitial tissue is not real. There was no change in the proportions of spermatogonia, spermatocytes, spermatids, and spermatozoa in mice exposed to 4 4r and 1 1r daily for 16 months as compared with nonirradiated controls although the quantity of spermatogenic tissue of the 4 4r mice was 60% of normal. After exposure to 8 Sr per day for 6 months there was failure of completion of spermatogenesis. This was associated with degeneration of Sertoli cells.

**Functional significance of the response of fatty metamorphosis of human liver to lipotropic therapy.** MURRAY FRANKLIN (by invitation), MELVIN R. SALK (by invitation), HANS POPPER and FREDERICK STEIGMANN (by invitation) *Cook County Hospital and Hektoen Inst. for Medical Research*. Patients with fatty metamorphosis (4 "normal" fatty, 10 cirrhosis, 2 toxic hepatitis), established by needle biopsy, were subjected to a series of liver function tests. The "normal" fatty group revealed essentially normal function. Almost all function tests in the cirrhotic group were pathologic. The hepatitics revealed less functional abnormalities. The abnormal findings in the cirrhotic and hepatic group were due to their intrinsic

pathology This confirms that fatty changes as such do not necessarily impair function

Lipotropic therapy (methionine, cystine and choline, hog stomach powder, liver powder) was instituted in 10 cirrhosis, 3 "normal" fatty and 1 toxic hepatitis for at least one month This resulted in clinical improvement of 7 of the cirrhotic patients and of all the "normal" and hepatic patients The laboratory findings in the cirrhotic group revealed greatest improvement in the albumin/globulin ratio, serum bilirubin and alkaline phosphatase, whereas, thymol turbidity improved least Most abnormal chemistry findings in the hepatic group attained normal values

In 7 cirrhotics, 2 "normal" fatty, and 1 hepatic, a repeat biopsy after therapy was performed and invariably revealed disappearance of fat, usually associated with improved morphologic appearance of the liver cells However, in the cirrhotic group, periportal fibrosis and cellular infiltration increased in 7 cases, improved in one

Lipotropic therapy was therefore successful in causing fat removal and functional improvement, however, in cirrhotics, mesenchymal changes usually progressed This is significant in evaluation of lipotropic therapy in the treatment of cirrhosis [Supported by a Grant from the Dr Jerome D Solomon Memorial Research Foundation]

Polysaccharide complex in individual follicles of the thyroid gland of the rat ISIDORE GERSH (introduced by Granville A Bennett) *Dept of Pathology, Univ of Illinois College of Medicine* Levine showed that the thyroid gland is very rich in hyaluronidase activity, and that the enzyme alters the viscosity of colloid The search for the enzyme substrate in the colloid was undertaken with a method for visualizing polysaccharide which was developed by Hotchkiss With this method, polysaccharide was found to be present in the colloid of thyroid follicles, regardless of their state of activity This is based on a study of normal and hypophysectomized rats and, of rats treated with potassium iodide, thyrotropic extract of the anterior lobe, or with sulfaguanidine Evidence supporting the hypothesis that at least a part of the visualized polysaccharide represents hyaluronic acid has been obtained Quantitative studies of the concentration of the polysaccharide complex in the colloid of individual follicles are in progress

Experimental alteration of the ability of tumor cells to lyse plasma clots *in vitro* PAUL GOLDBABER, IVOR CORNMAN and RICHARD A ORMSBEE (introduced by Cornelius P Rhoads) *The Sloan-Kettering Inst for Cancer Research, New York, N Y* Maximow slide cultures of mouse Sarcoma 180 were set up with various concentrations of aqueous humor and chicken plasma in the clot Even when satisfactory growth occurred no lysis

of the clot appeared in any of these preparations over a 1 day period The most extensive and vigorous growth was obtained with concentrations of aqueous humor + chicken plasma of 1:1 and 1:2 Normal growth of the tissue for a period exceeding 4 days has not been obtained

In the roller tube, lysis of aqueous humor + chicken plasma clots occurred when mammalian serum or aqueous humor was present in the supernatant fluid Further experiments showed that chicken serum could prevent the lysis, which occurred when aqueous humor or mammalian serum was present either in the supernatant fluid or in the clot Similar results have been obtained with several mouse tumors When the Rous chicken sarcoma was used, lysis of the clot was prevented by the presence of mammalian serum and accelerated by the presence of chicken serum

The current investigations are directed toward the determination of the mechanism by which tumor cells are able to lyse chicken plasma clots in the presence of mammalian serum or aqueous humor

Recovery of poliomyelitis virus from the throat during the incubation period F B GORDON (by invitation), FRANK M SCHABEL, JR, (by invitation), ALBERT E CASEY, and WILLIAM I FISHER (by invitation) *Dept of Bacteriology and Parasitology, Univ of Chicago, and the Chicago Health Dept* During epidemiological studies on poliomyelitis in Chicago in the summers of 1945 and 1946, specimens were taken from the throat and mouth of five children who later developed poliomyelitis Pools of two to five daily specimens from each child have been tested for the presence of virus by monkey inoculation Virus was recovered from three children, the pooled specimens representing periods of collection from the day of onset to the fourth, fifth or sixth day before onset

The epidemiologic significance of poliomyelitis virus in the throat will be briefly discussed

Iron uptake in 750 cases of human pregnancy using the radioactive isotope  $Fe^{59}$  P F HAHN, ELLA LEA CAROTHERS (by invitation) R O CANNON, (by invitation) C W SHEPPARD (by invitation), W J DARBAY, M M KASER (by invitation), G S MCCLELLAN (by invitation), and P M DENSEN (by invitation) *Depts of Biochemistry, Medicine, Obstetrics, and Preventive Medicine, Vanderbilt Univ Medical School, Nashville, Tennessee* Without any selection of cases white women admitted to the Obstetrics out-patient clinic were fed single doses of iron tagged with the radioactive isotope ( $Fe^{59}$ ) The iron was stored as

<sup>1</sup> This work was carried out under grants from the Nutrition Foundation, Rockefeller Foundation, and the Tennessee State Department of Health

<sup>2</sup> Contribution from the "Vanderbilt Cooperative Study of Infant and Maternal Nutrition"

ferric chloride until ready for administration. Immediately before feeding an excess of cevitamic acid was added to reduce the iron to the ferrous form. It was given by mouth and the time of administration was usually midway between meals. Duplicate blood samples were drawn about two weeks to one month later. The blood was centrifuged for 35 minutes at about 3,000 rpm and the hematocrit read. Plasma was discarded or used for other studies. Radioactivity was measured by means of a thin mica window, bell type Geiger-Müller counting tube in conjunction with a counting rate meter. The assumption was made that all the absorbed iron was present in the red cells of the maternal or fetal organism.

Dosage levels of iron were varied from 2 to 50 mg, at least 50 women being fed at any given level of intake. Between 2 and 18 mg dosage levels there were no apparent differences in the percentage uptake. The overall average uptake at these intake levels was 28.5%.

It was found that the percentage uptake of iron increased as gestation progressed. During the first quarter of gestation the average uptake was 17%, while during the last quarter it was 36%.

In about 100 cases studied in which cord blood and maternal blood were both obtained at delivery, it was found that the fetus took up about 10% as much as the maternal organism.

Local vascular phenomena induced in skeletal muscle by acute ischemia. JOHN W. HIRMAN (introduced by D. Murray Angevine), *Dept. of Pathology, Univ. of Wisconsin Medical School, Madison, Wisconsin*. It had been learned previously that with complete unrelieved ischemia significant lesions commenced to appear in skeletal muscle after a period of four to six hours. It has since been found that release of the ischemia even after a period of three hours is followed by extensive lesions, seemingly out of proportion to the period of ischemia. Release of tourniquets from rabbits' hind legs ischemic for between two and twelve hours is followed immediately by extensive edema. Several weeks later there is wasting in those with less than four hours, and gross infarction in those with more than four hours ischemia. Arterial spasm is excluded by direct palpation of the pulse, penetration of fluorescein, and arteriography with thorotrast. With the normal contralateral muscles as control, intravenous injection of two per cent Tetrabromophenol sulfonphthalein is followed by rapid entrance into, but abnormally slow elimination from, muscles ischemic for less than four hours. It penetrates very slowly and is very tardily eliminated from those ischemic for longer periods. Histologically the capillaries are distended with congested erythrocytes and muscle fibers are widely separated, this indicates capillary leakage, and stasis, with resultant stag-

nation, which perpetuates the damage initiated by ischemia. These studies support the belief that the progressive development of muscular lesions due to ischemia, despite relief of major vascular obstruction, is because of injury to the intimate vasculature.

A quantitative hypothermal method for production of local injury to tissue. GEORGE M. HASS and C. B. TAYLOR (by invitation), *Dept. of Pathology, Presbyterian Hospital, Chicago 12, Illinois*. Local necrosis of tissue can be produced rapidly and quantitatively by use of an instrument cooled to a low temperature by internal expansion of carbon dioxide or flow of cold liquids. The cooling element of the instrument is flat and circular, so that when it is applied to the surface of an organ or tissue, cylindrical lesions are produced. The diameters of the lesions can be varied from 2 mm to 25 mm by using cooling elements of comparable diameters. The depths of lesions can be varied from 1 mm to 13 mm by varying the time of contact of the cooling element with the tissue. Volumes of injured tissue can be accurately determined by measurement. Lesions of identical size and location may be reproduced in successive experiments. Lesions have been produced in cartilage, bone, skin, skeletal muscle, vascular walls, heart, liver, kidneys and brain of rabbits. Necrosis is uniform throughout the lesions and there is a sharp line of demarcation between non-viable and normal tissue at the periphery. Suppuration does not occur and hemorrhage is never found except around blood vessels in lesions of the brain. Organs and tissues can be progressively and selectively destroyed in a manner which is not possible by other methods such as cauterization, vascular ligation, or surgical excision.

Cancer cells in prostatic secretions. PETER A. HERBERT (introduced by Hobart A. Reimann), *Dept. of Pathology, Jefferson Medical College, Philadelphia*. Secretions are secured by massaging the prostate in the usual manner. They are collected directly upon three clean slides. Each is covered with a separate slide and by direct pressure and to and fro movement of the upper slide thin smears are prepared. The slides are pulled apart, fixed while still wet in equal parts of 95% alcohol and ether, stained by the Papanicolaou technique, and examined for cancer cells. The latter are variform and different sufficiently from normal prostatic epithelium to permit a diagnosis of carcinoma. Neoplastic cells are present as single cells, in small clumps or in sheets. They are usually larger than normal cells. Their borders are always indefinite, irregular and frayed. The cytoplasm is imperceptible, scanty or abundant and appears light gray, yellowish green or rusty. Sometimes it is solid while at other times it is reticulated or even vacuolated. The nuclei are sharply defined,

round or oval, relatively large, and intensely hyperchromatic or somewhat washed out and vesicular. The latter often contain nucleoli. In 100 patients examined by this method there were 20 with carcinoma of the prostate. A cytology diagnosis of cancer was rendered in 17 of these cases (85%). Present indications are that this procedure will be of value in equivocal or unsuspected cases of carcinoma of the prostate.

**Pathological changes produced by inhalation exposures to mono-chloro-mono-bromo-methane.** BENJAMIN HIGHMAN (introduced by R. D. Lillie) *National Inst. of Health*. Several series of white mice were given 1 to 5 successive daily 7-hour inhalation exposures to mono-chloro-mono-bromo-methane ranging from 1500 to 3300 p.p.m. (LD<sub>50</sub> in 72 hours for mice is approximately 2300 p.p.m.). Several animals of each series were killed for histological study immediately and at intervals following completion of each of 1 to 5 such exposures. The most constant pathological changes were fatty degeneration of the liver, kidney, and heart. Generally, these changes were most marked in mice killed 24 hours after the end of the first exposure and were absent in those killed more than 72 hours after the first exposure even though the animals continued to receive such exposures daily. Cloudiness of one or both eyes was noted in many mice a few minutes before they died. Lipoid depletion of the adrenal cortex was frequent only in animals killed immediately after the end of the first exposure. Pneumonitis was common in the mice exposed daily 24 to 72 hours after the end of their first exposure but was infrequent thereafter. Less common lesions were tubular necrosis and hemoglobin casts in the kidney.

Nineteen rats, 3 rabbits, and 2 dogs were killed after 67 daily exposures to 1000 p.p.m. of the compound. No significant changes were seen except for a slight increase of hemosiderin in spleen of the dogs and rats and some hemosiderin deposits and increase in fat in the kidneys of the dogs.

**Further observations on the possible role of cholesterol in arterial disease.** RUSSELL L. HOLMAN, *Dept. of Pathology and Bacteriology, L. S. U. School of Medicine, New Orleans*. Arterial lesions have been produced with regularity in dogs by feeding a specified high fat, low protein diet for two months or longer, then damaging their kidneys in any of several ways. The diet can be fed indefinitely and no lesions are ever observed until the kidneys are damaged. Any time after two months of this diet, experimentally induced renal insufficiency is regularly followed by arterial lesions.

The dietary factor is a lipid substance that is contained in, but is not unique to, cod liver oil, is heat stable, is not readily oxidized, and is not vitamin A or vitamin D.

The lesions—whose closest human counterparts are periarteritis nodosa and rheumatic arteritis—have been observed as early as four days after the production of renal injury and have been found in large elastic arteries, in muscular arteries, and in arterioles in practically every organ and tissue of the body, excepting the kidney and the liver. These lesions can be prevented or retarded by vitamin E and by cholesterol, either of which can be fed simultaneously with the diet or started up to three days after renal insufficiency has been produced. This latter finding eliminates the possibility that cholesterol interferes with the absorption of the "dietary factor" and augments the suggestion made before this society last year, namely, the primary role of cholesterol may be protective.

Further studies on experimental periarteritis nodosa with reference to variations in blood pressure and electrocardiographic changes. HOWARD C. HOOPS (by invitation) and WILEY T. MCCOLLUM (by invitation) *Dept. of Pathology, The School of Medicine of the Univ. of Oklahoma*. Previous observations that rabbits which received large doses of horse serum intravenously developed, in addition to periarteritis nodosa, marked hyperplasia of the juxta-glomerular apparatus suggested that hypertension might have been concomitant. For this reason and because periarteritis nodosa has been observed in animals with induced hypertension, blood pressures were determined twice weekly before, during and after the period in which rabbits received horse serum intravenously. Electrocardiographic tracings were taken also during this time in view of the fact that focal myocarditis had been observed to occur under these conditions. Gross and histopathologic changes are correlated with the observed variations in blood pressure and electrocardiographic changes.

**Conversion of acute into chronic leukemia.** RABHAEL ISAVES, *Michael Reese Hospital, Laby of Hematology*. The average length of life of a patient with acute leukemia is given as six weeks. Occasionally spontaneous remissions develop, with subsequent relapses. Data are given of 6 patients with acute (blast) leukemia in whom remissions were produced and the blood picture changed to that of a chronic type after feeding a solution of crude tyrosinase daily. The patients lived from 5 months to 1 year, the shorter ones having had their therapy discontinued. In chronic myelogenous leukemia, the therapy was followed by a decrease in the number of blasts and a relative increase in the number of mature forms. Tyrosinase converts tyrosine into melanin, a substance which increases in the skin of leukemia patients successfully treated with x-ray or arsenic (Fowler's solution).

The influence of injections of homologous

hemoglobins into normal and dehydrated animals  
 JOSEPH J LALICH *Dept of Pathology, Univ of Wisconsin Medical School, Madison, Wisconsin*  
 Homologous hemoglobins were injected in single doses intraperitoneally into rats and guinea pigs which were given food and water as desired. Three groups of rats received 5, 6 and 7 grams/kg. Four groups of guinea pigs were given 1, 2, 3 and 3.5 grams/kg. In 16 rabbits water was withheld for periods of 1-3 days prior to intravenous injections of hemoglobin in quantities of 1-1.8 gram/kg in single or divided doses on successive days. During injections the rabbits were deprived of water. In 12 of 16 animals on which necropsies were done after the 4th day there were visible dark brown flecks measuring 1-2 mm across on the surface and in the cortex of the kidney. Prior to the 4th day the kidneys appeared congested. Microscopic examination of the kidneys demonstrated yellow or orange pigment casts in 12 of 13 animals. The casts were principally localized in the distal convoluted tubules. Associated with the casts there was dilatation of the tubules proximal to the obstruction. In only 4 of 13 kidneys was there minimal necrosis of tubular epithelium. In 14 rabbits the plasma NPN was elevated temporarily in 5 which survived and in excess of 200 mg per cent in 2 which died in uremia. In six the NPN remained below 42 mg per cent. It is felt, therefore, that hemoglobinuric nephrosis can be reproduced consistently in rabbits when dehydration precedes the intravenous injections of hemoglobin.

Effects of various protein diets on colloids (plasma protein and gum acacia) in the blood  
 RALPH E KAUTTI *Univ of Rochester and Childrens Hospital of Los Angeles*  
 Dogs, subjected to "chronic" hypoproteinemia by previous injections of gum acacia, were alternately placed on various high and low protein diets. During periods of high protein diet, plasma protein increases in both concentration and total amount and plasma acacia decreases both in concentration and total amount. During periods of low protein diet, the reverse takes place. A higher than average protein intake is necessary to show evidences of plasma protein release into the blood, adding further evidence that gum acacia interferes with plasma protein production. In such an animal subjected to plasmapheresis, considerably more gum acacia was removed from the blood than had been present at the start, indicating that gum acacia was being released into the blood from body stores (liver?). The evidence also suggests that both gum acacia and plasma protein can, under the circumstances, be returned to body stores from the blood.

The experimental production of acute pancreatitis  
 ROLF LIPP (by invitation) STEPHEN MADDOCK and DOROTHY JENSEN (by invitation)  
 Much evidence in the literature points to obstruction

of the duct in a secreting gland as the etiologic factor leading to acute pancreatitis. Experiments were undertaken to stimulate the pancreas with and without obstruction of the ducts. Cats were used. Some were starved, whereas others were fed two to four hours before the ducts were ligated.

Pilocarpine, eserine and acetylcholine, and secretin were used to stimulate the pancreas. The animals were sacrificed 24 hours to 7 days later. Fat necrosis was a uniform finding in all animals that had had the ducts ligated and the gland stimulated. Stimulation after a meal yielded the most extensive damage to the pancreas. Secretin was more effective than the other agents in producing pancreatitis.

Acute pancreatitis in humans is due to obstruction of the duct in the presence of a secreting gland. A heavy meal acts as the stimulant in many cases. In others ingestion of alcohol is a causative factor in augmenting pancreatic secretion by stimulating HCl secretion and thence secondarily producing secretin in the duodenum. Obstruction of the ducts may be due to a stone, ascariis, spasm, edema or tumors. The common elements in all cases of acute pancreatitis are obstruction of the ducts and an actively secreting gland. [From *The Surgical Research Lab of The Boston City Hospital*]

The role of intensity in chronic irradiation with gamma and x-rays  
 EGON LORENZ and ALLEN B. ESCHENBRENNER *National Cancer Inst, Bethesda, and National Argonne Lab, Chicago*  
 LAF<sup>1</sup> mice were given daily whole body irradiation. In one experiment the daily dose was 88 r of gamma radiation given in 8 hours, in the second, the same daily dose was given in 15 minutes with x-rays. One group of mice of each experiment received a total dose of 300 r, another group a total dose of 600 r. Radiation injury measured by the decrease in testes weights, showed that the testes weight of the animals of the low intensity exposures was approximately 1.5 times greater than that of the animals of the high intensity exposures. The data obtained in these experiments may not be strictly comparable as x-rays and gamma rays were used and there might exist a "quality" difference not due to the physical measurement instrument used. A further experiment was set up in which only x-rays were used, the low intensity was obtained by increase in focus animal distance and increased filtration. One group of animals was exposed to 10 r in 137 minutes and the other group to the same dose given in 4 hours and 186 minutes 5 times per week to a total dose of 300 r. The weight of the testes of the low intensity group was 1.3 times greater than that of the high intensity group. The agreement with the previous experiments is satisfactory. The data indicates that an intensity effect exists in chronic whole body irradiation with pene-

trating rays, resulting in increase in radiation injury with increase in intensity for the same daily and total dose

**Constitutional factors in resistance to infection, the effect of estrogen on the pathogenesis of tuberculosis** MAX B LURIE, SAMUEL ABRAMSON<sup>1</sup> (by invitation) and MARVIN J ALLISON (by invitation) *The Henry Phipps Inst of the Univ of Pennsylvania, Philadelphia* Estrogen retarded the progress of tuberculosis at the site of inoculation in the skin and the dissemination of the disease in the internal organs as compared with that in rabbit litter mates of the same genetic constitution and of similar hereditary resistance to the infection The periodic, intravenous injection of chorionic gonadotropin, which induced successive crops of corpora lutea, accelerated the progress of the disease in the majority of highly inbred litter mates Physiologic quantities of progesterone and estradiol exerted no consistent effect on the process, nor did ovariectomy

Estrogen suppressed tuberculin sensitivity of the skin not only in animals with active disease but also in rabbits treated with heat-killed tubercle bacilli, but the sensitivity of the internal organs was not diminished Since chorionic gonadotropin also reduced skin allergy, this effect of estrogen was not the significant factor in its retardation of the disease Estrogen reduced the inflammatory irritability of the skin to unrelated noxious agents and markedly suppressed amyloid degeneration which is incidental to chronic tuberculosis Ovariectomy, chorionic gonadotropin and progesterone did not inhibit amyloidosis Chronic estrogen treatment induced a lymphopenia and was associated with a reduction in the weight of the adrenals There is some evidence that estrogen enhances the elimination of antibodies from their depots

It is suggested that estrogen retards the tuberculous process by sparing parenchymal degeneration and by mediating the release of antibodies through the dissolution of lymphocytes caused by the discharge of the adrenal cortical hormone [Added by a grant from the Commonwealth Fund The hormones were supplied by Dr Ernst Oppenheimer of the Ciba Pharmaceutical Products, Inc]

**Hypervitaminosis A in the dog** CHARLOTTE L MADDOCK, (by invitation) S BURR WOLBACH, STEPHEN MADDOCK and DOROTHY JENSEN (by invitation) *Department of Pathology, Harvard Medical School and The Surgical Research Lab, Boston City Hospital* Although hypervitaminosis A has been produced in various animals the response of the dog to excessive A has never been

reported In the present study a litter of 5 greyhound puppies, comprising 3 males and 2 females, was used The puppies were taken from the mother at two months of age and observed for a week After this interval the largest male and the larger female were singled out for excessive vitamin A administration while the others were kept as controls Vitamin A concentrate was fed daily to the experimental animals at a level of 300,000 I U per kilogram of body weight For the first 53 days all animals gained, but from that time on the experimental dogs showed a precipitous fall No spontaneous fractures were noted during the course of the experiment, but x-rays revealed excessive remodelling of the long bones The female was sacrificed on the 58th day, the male on the 69th Terminally, both showed a moderate exophthalmos, marked hyperesthesia of the skin and extreme tenderness of the extremities

Blood studies revealed vitamin A values in excess of 10,000 I U per cent and a drop in total cholesterol and lipid phosphorus No other significant changes were noted

The same changes in cartilage and bone described by Wolbach and Bessey in 1942 and again by Wolbach in 1946, in the rat and guinea pig were seen in the histological sections The remainder of the histological picture was essentially normal

**Protein metabolism studies in dogs with partial constriction of inferior vena cava** FRANK W MCKEE, PAUL R SCHLOERB and GARSON H TISHKOFF (introduced by George H Whipple) *Dept of Pathology, Univ of Rochester School of Medicine and Dentistry* The study of protein metabolism in dogs with constriction of the inferior vena cava is being undertaken to determine the ability of the animals to form extra protein on high and low protein diets in the presence of a severe chronic passive congestion of the liver Partial constriction of the vena cava above the diaphragm by means of a metal band is the experimental lesion Collateral circulation over the anterior abdomen is well developed six to eight weeks following application of the band Blood total proteins and albumin, ascitic fluid total protein and albumin, and total urinary nitrogen, are determined and form the basis for a study of protein metabolism Dietary nitrogen is controlled Experiments indicate that a low protein diet results in massive ascites with moderately high protein content and marked lowering of the plasma protein level, while a high protein diet produces only scanty ascites of high protein content and a recovery of high blood protein levels The experiment is essentially an internal plasmapheresis

<sup>1</sup> Further studies on the leukocytosis-promoting factor of exudates VALY MENKIN *Temple Univ School of Medicine, Philadelphia, Pennsylvania* The earlier studies of the writer have

<sup>1</sup> Asst Scientist (R), Tuberculosis Control Division, U S Public Health Service



demonstrated the presence of a leukocytosis-promoting factor in inflammatory exudates capable of reasonably explaining the mechanism of leukocytosis with inflammation. The factor is present in human exudates. The canine material is both active and innocuous when injected intravenously in human beings. This suggests the clinical application of this factor. As extracted, it is associated with the pseudoglobulin fraction of exudates, and it is very soluble in an aqueous medium. After several months the material, even though left in a desiccator *in vacuo* under phosphoric anhydride, gradually becomes insoluble, and this insoluble material is relatively inactive. However, if the saline suspension of the material is centrifuged, the supernatant fluid is found to contain the active LPF. The fluid is Biuret negative, and it is heat stable. The fluid can be evaporated to dryness on a steam bath, and then the newly obtained dried material is found to be also insoluble. Yet a suspension of this newly obtained material is potent in dogs. Tryptic digestion of fresh LPF fails as a rule to inactivate the factor. All these facts lend support to the view that the active principle is either a protein derivative, such as a polypeptide or an amino acid, or else that it is adsorbed on the pseudoglobulin fraction of exudates.

**Renal pathology incident to shock** VIRGIL H. MOON, *Dept of Pathology, Jefferson Medical College*. After death by secondary shock, the kidneys regularly show acute degenerative changes. These are seen after shock from wounds, surgery, burns, poisoning, intoxications, infections, heat stroke, asphyxia and from other causes. Similar changes are seen after experimental shock induced by various methods. The changes range from acute parenchymatous degeneration to necrosis, most marked when death has been delayed.

The kidneys are swollen, hyperemic and edematous. The capillaries are distended. The glomerular spaces may contain aluminous material. The cytoplasm of the tubular epithelium may be granular, vacuolated or may show cytotoxicity. It may contain acidophilic hyaline appearing granules or droplets. Nuclear changes include hyperchromatism, vacuolization, pyknosis and karyolysis.

Often the epithelium is desquamated. The lumina contain erythrocytes, epithelial cells, debris and casts of various kinds, often pigmented. The convoluted tubules are rather diffusely affected. I have not found the degeneration limited to any particular portion of the nephron.

Renal functional disturbance is manifested by oliguria, albuminuria, hematuria, casts, and by progressive azotemia. If sublethal shock continues several days, death often results from uremia.

The cause for epithelial degeneration and necrosis has not been shown. Toxic effects have been

suggested when shock has resulted from severe infections or from poisons. But in shock from heat stroke, lack of oxygen or from low barometric pressure, no toxic agent is implicated. Anoxia appears as the common factor in shock from diverse causes, probably it is an important agent in the renal effects described.

**Pathologic alterations resulting from the administration of 2,4-dimethyl-3-hydroxy-5-hydroxymethyl-pyridine**, an analogue of pyridoxine, CHARLES W. MUSHETT, (introduced by W. B. Castle) *Merck Inst for Therapeutic Research, Rahway, N. J.* 2,4-dimethyl-3-hydroxy-5-hydroxymethyl-pyridine (desoxyypyridoxine) has been shown by Ott (Proc Soc Exp Biol & Med 61:125, 1946) to be a potent inhibitor of pyridoxine in chicks. Experiments conducted in chicks, mice, rats, dogs and monkeys have demonstrated that this vitamin analogue produces atrophy and degeneration in the lymphoid organs, particularly in the thymus and spleen, and in the bone marrow. The peripheral blood picture reflected the changes in these hematopoietic organs. When administered to chicks on an adequate diet, the drug caused a reduction in spleen size almost comparable to that produced by a pyridoxine free diet. Although desoxyypyridoxine aggravated certain symptoms of the pyridoxine deficiency syndrome in puppies, it delayed the onset of other symptoms. Single large doses of the drug brought about a state of hyperexcitability followed by convulsions and death. The significance of these findings relative to the treatment of tumors of the lymphoid tissue will be discussed.

**Pathological changes produced by feeding of chloroquine (SN-7618) to rats** ARTHUR A. NELSON and O. GARTH FITZHUGH (by invitation) *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Twenty-one day old albino rats, 20 to the group, were fed chloroquine at levels of 1000, 800, 400, 200 and 100 p.p.m. in a stock diet. Eighty-six treated and 15 control rats were examined microscopically in detail. Animals receiving 1000 p.p.m. survived 13 to 21 weeks and uniformly showed marked fibrous replacement of cardiac muscle, similar but slightly less damage in voluntary muscles, and moderate centrilobular hepatic necrosis and fibrosis. Other lesions, less severe or less frequent, were hunched back, paleness of viscera, cardiac atrial thrombosis, testicular atrophy, and in several locations cytoplasmic basophilia and pigmentation, and the presence of foamy macrophages. With each decrease in dosage level, damage resulting from chloroquine was lessened, at 400 p.p.m. it was moderate, at 200 p.p.m. slight, and at 100 p.p.m. questionable. At 400 p.p.m. or less in the diet, some animals survived the full two year experimental period.

The above lesions show considerable similarity to those reported following similar levels of quina-craine feeding (J Pharm & Exper Therap 85 207, 1945). The chief difference is in the lack of massive hepatic necrosis with chloroquine, muscle lesions are, however, somewhat greater. Pigmentation, basophilia and foamy macrophages are generally similar. For rats, chloroquine appears from the pathological standpoint to be about as toxic as or possibly slightly less toxic than quina-craine.

**Tissue element in the origin of neoplasms**  
**Morphologic evidence that certain neoplasms have multicellular origin** ANDERSON NETTLESHIP *Dept of Pathology, Alexander Blain Hospital*. Extremely early carcinomas from the following tissues were studied: carcinoma in situ in the breast, carcinoma in situ of the stomach, epidermoid carcinoma of the skin and cervix uterus. In all cases it was possible to show that a focal area, the cells of which are in approximately the same stage of neoplastic development, was the origin of this neoplasm rather than a single cell. The tissue background out of which cancer arises was also studied. This, too, contributes to the evidence for the origin of cancer from a tissue which shows widespread tissue atrophy and a multicellular background.

**The action of crystalline tetanal toxin in white Swiss mice** LOUIS PILLMLER (by invitation) and WILLIAM B. WARTMAN *Inst of Pathology, Western Reserve University and Department of Pathology, Northwestern Univ Medical School*. The isolation and crystallization of tetanal toxin has made it desirable to reinvestigate some of the properties of this toxin. Accordingly, this report deals with an investigation of 1) the clinical behavior of white mice given varying amounts of crystalline toxin intramuscularly, 2) the influence of the dose of toxin on the length of the incubation period and on the time required for death, and 3) the pathological lesions produced by crystalline tetanal toxin.

Intramuscular administration of 0.000013 gamma of crystalline tetanal toxin nitrogen produced the classical signs of tetanus in white mice weighing between 15 and 20 grams. Incubation period was about 30 hours and death occurred in 96 hours. This dose of toxin is one mouse MLD.

Intramuscular administration of 6.4 gamma of crystalline tetanal toxin or 500,000 MLD led to appearance of symptoms within 30 minutes and death in 60 minutes. The chief clinical signs were fixation of the muscles of the thorax and abdomen, respiratory embarrassment, increased muscular tonus and asphyxia.

These results indicate that, in white mice injected with crystalline tetanal toxin, the so-called incubation period is dependent upon the amount of toxin administered and can be varied at will.

No pathological lesions were produced in white mice which received single doses of crystalline tetanal toxin ranging from 0.25 MLD to 500,000 MLD and which lived from one hour to 28 days after injection of the toxin. Similar results were obtained when repeated sublethal doses of toxin were given.

**Electron microscope studies of blood cells in the hematopoietic organs and inflammatory exudates of man** JOHN W. REBUCK and HELEN L. WOODS (introduced by F. W. Hartman) *Dept of Labys, Henry Ford Hospital, Detroit, Michigan*. Blood cells of the lymph nodes, spleen, and bone marrow were imprinted upon glass slides covered with Formvar 15-95 films. The preparations were at once frozen by a modification of the Altmann-Gersh freezer technique and, while still frozen, were dehydrated *in vacuo*. The films were transferred to screens by a modified stripping technique in which the cells were retained intact. Both surgical biopsies and autopsy specimens have been examined in this manner. Lymphocytes, neutrophils, neutrophilic myelocytes and their precursors, red corpuscles and the later stages of erythroblasts were observed.

Lymphocytes, lymphocytogenous macrophages, macrophages and neutrophilic leukocytes of the inflammatory exudate of man were obtained by imbedding Formvar covered screens in the corium of the forearm. The cells which migrated to the undersurfaces of the screens were likewise quick-frozen and dehydrated *in vacuo*.

Electron micrograph studies of the detailed structure of the cytoplasm, neutrophilic granules, nucleoli, and nuclear cytoplasmic interfaces are presented.

**Folic acid deficiency in the monkey** JAMES F. RIVKIN and LOUIS D. GREENBERG (by invitation) *Depts of Pathology and Pharmacology, Univ of California Medical School, San Francisco*. Using the diet and supplements described previously (Federation Proceedings 5 222, 1946), folic acid deficiency has been studied in rhesus monkeys. Our observations are similar to those of Day et al (J Biol Chem 161 45, 1945), and Waisman and co-workers (J Nutrition 26 205, 361, 1943). Generally the animals developed leukopenia, anemia, diarrhea, gum ulcerations, severe anorexia and cachexia. If the depletion was not carried beyond a critical point, the animals showed a dramatic response to the administration of synthetic pteroyl glutamic acid. A consistent pathological manifestation found at autopsy was the presence of severe and extensive ulcerative colitis. While this at times was associated with a dysentery bacillus in other instances it was not. Colitis appears to be an essential part of the deficiency syndrome.

During the course of this investigation the level

of L casei factor in the blood and the various elements of the blood were followed by microbiological assay. The range of values for folic acid deficient animals are as follows: whole blood 2.3-4.9, plasma 2.5-5.3, unwashed red cells 1.6-3.4 all expressed as  $\gamma$  per 100 ml. For the controls the corresponding values were: whole blood 2.5-5.3, plasma 2.7-5.1, unwashed red cells 1.3-4.0. The concentration of the vitamin in the buffy coat was approximately 10 fold that of the whole blood or plasma. No alteration of the folic acid content of blood or any of its elements was observed in the deficient state. Red cells washed with isotonic saline yielded values approaching zero. A good portion of the folic acid removed by washing can be accounted for in the washings. It would seem probable that the folic acid is adsorbed on the red blood corpuscles.

**The metabolism of some estrogen degradation products.** ALBERT SEGALOFF *The Alton Ochsner Medical Foundation, New Orleans, Louisiana*. Our previously reported studies on the metabolism of estrogens in the rat have been extended to include some degradation products of estrogens. As before, the method of intrasplenic injection was employed.  $\beta$ -estradiol, Westerfeld's Lactone and bis dehydro doisylnolic acid (studied as the sodium salt) and its 3 methyl ether were studied.

$\beta$  estradiol and Westerfeld's Lactone were both inactivated in the liver. However, their low estrogenic potency and the limitations of solubility precluded an exact measure of the degree of inactivation.

The methyl ether of bis dehydro doisylnolic acid proved to be about as potent in producing vaginal estrus as diethylstilbestrol when both were given by subcutaneous injection. However, when they are given intrasplenically a striking difference is noted in that less of the methyl ether of bis dehydro doisylnolic acid is required to produce vaginal estrus than when it is administered subcutaneously. Heretofore we have noted this type of metabolic response only in synthetic proestrogens, all of which contained a phenyl group.

Thus, it appears that various degradation products of the natural estrogens are handled by the rat's liver in strikingly different ways.

**The use of colloidal radioactive gold in medical therapy.** C. W. SHEPPARD (by invitation) and P. F. HAHN *Dept of Biochemistry, Vanderbilt Univ.* The experimental use of intravenously administered colloidal sols containing artificially radioactive isotopes in the therapy of diseases of the lymphoid system has been explored.<sup>1</sup> The isotope now being investigated is radioactive gold,  $Au^{193}$ . This isotope has an ideal half life ( $2\frac{1}{2}$  days) per-

mitting close control of radiation received by the patient without large decay losses in shipment. No detectable long lived material is present. The chemistry of gold colloids is familiar and sols of great stability are prepared with ease. When given in this form no toxic symptoms of any due to the metal are observed. The amount of gold per dose is always less than five milligrams. Although the biological effect should be predominantly due to the beta rays enough gamma radiation is emitted to permit external tracing of the material in the patient with a directional Geiger-Muller counter. These rays are soft enough to be easily screened with relatively light lead shields, permitting safe handling in the laboratory and ease shipment. The radioactive material is prepared by the Clinton Laboratories in the chain-reacting uranium pile at Oak Ridge. A single biologically effective dose costs less than \$4.00. In addition to intravenous administration surface lesions have been injected locally, producing a striking improvement and decrease in size. [This research was made possible by a grant from the Donner Foundation.]

**Development of complete marrow in adult animals.** BERNHARD STEINBERG and VIRGINIA HUFFORD (by invitation) *Toledo Hospital Inst of Medical Research*. Development of marrow cells has been studied in fetal life, in young animals and in tissue culture. Regeneration was observed after hypoplasia by chemicals, starvation and disease. In this study, regeneration of marrow including stroma, fat spaces and cells is presented. Marrow was removed mechanically avoiding the systemic effects incident to previous methods.

The marrow of one or both tibiae of rabbits was extirpated. A small opening was drilled at one end and a large aperture at opposite end of bone. The marrow was flushed out with oil and saline with syringe and cannula inserted into small aperture. Pipe cleaners were passed through the shaft until washings came clean. One or both epiphyseal ends were cleaned out and packed to prevent reformation of marrow.

Sixty bones in 44 rabbits were extirpated. Animals were killed between one and 60 days. Absolute and relative number of cell types were counted in normal and regenerated marrow. Rapidly and extent of fat space and reticulum formation, refilling of shaft with marrow and reestablishment of absolute and relative cell content were determined.

Regeneration was neither uniform in the same shaft nor in different animals. Marrow reformation began from endosteum with offshoots of primitive reticular cells and bone spicules. Fat spaces appeared to be formed by approximation of reticular cells and appearance of cytoplasmic vacuoles. Presence of fat spaces was prerequisite to formation of myeloid elements. Granulocytes, erythro-

<sup>1</sup> Hahn, P. F. and Sheppard, C. W. *Southern Med J* 39: 555, 1946.

cytes and megakaryocytes appeared to be derived from a single primitive reticular cell

**Carcinogenic substances in extracts of human lungs** PAUL E. STEINER, D. WARREN STANGER (by invitation) and MIRIAM N. BOLYARD (by invitation) *Dept. of Pathology, The Univ. of Chicago*. Sixty-two nonsaponifiable lipid extracts from 106 human lungs were tested for carcinogenic activity in 474 mice of C57 Black and our albino strains. The lungs were from cases of primary pulmonary cancer, the noncancerous contralateral lung, no malignant tumor, cancer primary elsewhere in the body, and stillborn infants. Six sarcomas were induced at the sites of injection of four different extracts. This was a 38.6 per cent yield calculated on the basis of number of tumors which occurred in mice alive in the experiments with active extracts when the first tumor appeared. The per cent yield, calculated on the basis of number of tumors in mice surviving at six months, was 18.8. In addition, the incidence of lymphatic tumors in C57 Black mice was possibly increased over normal. The sarcogenic extracts were derived from a nontumorous lung opposite a primary carcinoma, the noncancerous lungs in a case of carcinoma of the prostate, a case of malignant hypertension, and pooled lungs from stillborn infants. The presence of tumor inducing activity in lungs of infants who had not inhaled air indicates that the sarcogen was probably exogenous. [*This investigation was aided by a grant from the Commonwealth Fund*]

**The rate of nitrogen elimination through the lungs in relation to susceptibility to decompression sickness** CHARLES D. STEVENS, HENRY W. RYDER and EUGENE B. FERRIS (introduced by M. A. Blankenhorn) *Dept. of Internal Medicine, College of Medicine, Univ. of Cincinnati*. Individuals differ in the rates at which they eliminate nitrogen from their lungs while lying down breathing oxygen at ground level. In young men these differences are related to differences in body weight. Individuals with high rates of nitrogen elimination per unit of body weight are less susceptible to decompression sickness than those with low rates. In the prediction of the relative individual susceptibility of young men to decompression sickness either from nitrogen elimination data or from data on simulated flights or from body weight data, there remains at best 60% to 90% of the element of chance in the placement of the individuals.

For each elimination six samples were routinely

collected by a rebreathing technique during the period of 1 to 20 minutes after beginning oxygen breathing. Of the 85 eliminations of 37 individuals thus measured, the first two eliminations of 31 individuals showed a correlation of  $r = +0.7$ . Correlation coefficients were determined between the average amount of nitrogen eliminated and body weight ( $r = +0.68$ ), height ( $r = +0.44$ ), CO production during nitrogen elimination ( $r = +0.43$ ), age ( $r = -0.02$ ), and several calculated factors.

A plot (suggested by Claude Emmerich) of the logarithms of cc of nitrogen eliminated/kg/minute for each sample against the logarithms of the mid points of the sampling intervals expressed in minutes after initiation of oxygen breathing, falls on a straight line within the sampling error.

**Plasma and red cell radio-iron following intravenous injection** Sterile abscesses in normal and anemic dogs. CHARLES L. YULE, CHAUNCEY G. BLA (by invitation) and JOHN C. WELLS (by invitation) *Dept. of Pathology, Univ. of Rochester School of Medicine and Dentistry*. Normal dogs and those rendered anemic by repeated bleeding have received small tracer doses of radio active iron (1.5-2.5 milligrams) by intravenous injection. Total and radioactive plasma iron levels and red cell utilization have been studied before, during and after the institution of single and repeated sterile turpentine abscesses in both groups of animals. The disappearance of radio-iron from the plasma is similar in normal animals with abscesses and in anemic animals with or without abscesses, being almost complete in from 4-8 hours. Normal dogs, however, without abscesses retain relatively large amounts of the injected iron for as long as 48 hours in some instances. Red cell utilization of the isotope is measured by its incorporation into circulating hemoglobin and can be readily detected in all groups of animals as early as 2 to 4 hours after injection and rapidly increases until a plateau is reached between 7 and 10 days. Although maximum red cell utilization is affected little if at all by the presence of a single, well developed sterile abscess at the time of injection, decreases of about 75% in utilization are found when repeated abscesses are induced during the following 2 week period. This indicates that factors other than decreased gastro-intestinal absorption can be responsible for diminished red cell formation in this type of infection. Pus aspirated from the abscesses was found to contain only insignificant amounts of radioactive iron.

## THE AMERICAN INSTITUTE OF NUTRITION

ELEVENTH ANNUAL MEETING

Chicago, Ill., May 18, 19, 20, 21, 22, 1947

(For possible corrections in any of the following abstracts see the next issue)

Evaluation of the amino acid requirements of the chick H J ALMQUIST *Research Labys, F E Booth Co, Inc, Emeryville, Calif* Available data on the amino acid requirements of the chick have been subjected to a critical analysis Amino acid intake and growth of chicks have been found to exhibit fundamental and surprisingly uniform relations The region of negative rates of gain is a linear continuation of the region of positive rates The curves relating rate of gain to amino acid concentration in the diet for various indispensable amino acids converge to a common negative rate at which all protein synthesis must cease

The same maximum requirement levels are obtained with whole proteins diets as with hydrolyzed proteins or amino acids diets, although maximum rates of gain attained with the various diets may differ considerably As the level of an indispensable amino acid in the diet decreases below optimal, the growth differences of whole proteins and amino acids diets disappears

Rates of gain substantially higher than the limiting negative rate are evidence that synthesis of protein, and of any absent amino acid, is taking place The sign and magnitude of the rate of gain is dependent upon the relative speeds of protein synthesis and destruction in the animal Various factors responsible for the differences in rates of gain with whole proteins and free amino acids diets are discussed

The effect of milk on the incidence and extent of dental caries in the cotton rat E PORTS ANDERSON (by invitation), J KNOX SMITH (by invitation), C A ELVEIEM, and PAUL H PHILLIPS *Dept of Biochemistry, Univ of Wisconsin, Madison* Studies were made on the effect of milk on dental caries in the cotton rat as part of a general investigation on nutritional phases of the dental caries problem In previous work animals fed on a diet of whole liquid milk had been found to be completely free of carious lesions, showing greater protection than that observed with any other ration Experiments were therefore conducted in an attempt to determine the degree and nature of this protection

Fermentable sugars such as sucrose, glucose, and dextrinmaltose have previously been found to be highly cariogenic when fed as the carbohydrate portion of dry rations Each of these sugars was homogenized into liquid milk at a level of 10 per cent These rations produced a very low incidence and extent of carious lesions

Milk supplements were given to animals being fed the cariogenic control ration (a sucrose ration)

and here also it was found to be protective Caries indices on this diet were about half as high as those on the unsupplemented control ration Results of feeding such supplements to animals on another cariogenic diet more closely resembling a human diet in composition will be reported

In order to eliminate the fluidity factor studies are being made with various milk solids rations, namely, synthetic milk solids, dry whole milk (Klim), and dry skim milk plus butter

The biological value of amino acid mixtures in the rat JOSEPH T ANDERSON (introduced by E S Nasset) *Dept of Physiology and Vital Economics, Univ of Rochester* The biological value (B V) of amino acid mixtures was determined in mature rats fed by stomach tube twice daily Each experiment consisted of a seven day N free period followed by a seven day period on amino acid mixture, the urine N of the sixth and seventh days being used in each case Before and between experiments the rats were fed an isocaloric diet containing whole egg supplying enough N to restore in three weeks the N lost by the animals in two weeks on experiment

A "complete" amino acid mixture was made up to simulate egg in that it contained (per gram of total N) the same amount of the natural isomer of each of the ten essential amino acids as found in whole egg protein by Edwards et al (*J Nutrition* 32:597 (1946)) The remainder of the mixture was made up of the unnatural isomers of the six amino acids used as dl forms plus 1(+) glutamic acid (20.5% of N) This "complete" mixture was compared with a "low isoleucine" mixture in which the dl isoleucine was reduced to  $\frac{1}{3}$  and the N so omitted replaced by glutamic acid

The "complete" amino acid mixture gave B V results of 135% and 138%, the "low isoleucine" mixture a B V of 112%, the significance of the difference corresponding to  $P < 0.01$  Urine N on either amino acid diet was lower than on the N free diet The absorbed N necessary to give N equilibrium was significantly greater on the "low isoleucine" diet than on the "complete" diet

It appears likely that in the "low isoleucine" amino acid mixture a mild relative deficiency of isoleucine exists and that the extent of the deficiency can be measured by the reduction of B V and the increase of absorbed N required for equilibrium [acknowledgment is made to Swift and Company and the Navy Department Office of Naval Research for grants which supported this work in part and to Hoffman LaRoche, Inc for a gift of scieral amino acids]

Survey of the sodium and potassium content of foods and waters by the flame photometer CHARLES E. BILLS, FRANCIS G. McDONALD (by invitation), WILLIAM NIEDERMEIER (by invitation) and MELVIN C. SCHWARTZ (by invitation) *Research Lab., Mead Johnson and Co., Evansville, Ind.* Quantitative flame photometry is so new that little has been reported on its usefulness with biological materials. A Perkin-Elmer flame photometer was calibrated with spectroscopically pure salts, and exploratory studies made to ascertain the best working conditions. Relatively concentrated solutions gave curvilinear responses, but with 0-10 ppm of Na or K the response was linear and scarcely affected by foreign solutes. Either element can be determined in the presence of several thousand quantities of the other by applying a small correction factor. Extraordinary precautions must be taken against adventitious entry of the element studied, e.g., the abrasion in turning a glass stopper may release ruinous amounts of Na. The necessary precautions, once recognized, are not difficult to observe.

Dilutions of urine, serum, sweat, whey, and fresh milk are analyzed without ashing. Ashed materials are dissolved in dilute HCl. About 300 foods and the waters of 100 cities were analyzed. In comparison with published data by the old methods our findings were in fair agreement for K. They agreed also for Na when the amount of this element was substantial, but were lower when it was small. The lower the sodium content, the greater was the disparity, until it amounted to more than 100 fold for foods of extremely low Na content. The defect in the old methods lies in the estimating of Na by difference, the error becoming enormous as the quantity approaches zero. Flame photometry is a revolutionary advance in quantitative analysis.

Normal activity and economy of food utilization as affected by dietary fat ALAN BLACK (by invitation) and R. W. SWIFT *Dept. of Animal Nutrition, School of Agriculture, Pennsylvania State College*. Respiration experiments were conducted by the carbon-nitrogen balance method, with 24 relatively mature male albino rats as subjects, to investigate the relation of normal voluntary activity on the total heat production of animals consuming diets of different fat content. One-half the experimental subjects were fed a diet of 2% fat content, the other half received a 30% fat diet—each diet being so compounded and fed that all animals received the same amount of protein, energy and vitamins. The daily food intake was constant and slightly in excess of maintenance.

Carbon dioxide production was measured continuously for two consecutive days in respiration chambers which were sufficiently large to accommodate the usual experimental type cage. After

completing a series of two 2 day respiration measurements on each rat, the assignment of the diets was reversed and the same procedure repeated.

Although final results are dependent upon excreta analysis not yet completed, it was found that the rats on the high fat diet produced 15% less CO<sub>2</sub> than those on the low fat diet. Almost identical results were obtained after reversal of the diets.

This difference in CO<sub>2</sub> production is of the same magnitude as the difference in heat increments obtained previously in similar work at this laboratory using mature rats with voluntary activity excluded.

Comparative biological availability of iron in the form of ferrous sulfate or ferric orthophosphate HAROLD BLUMBERG and LARON ARNOLD (by invitation) *Sterling-Winthrop Research Inst., Rensselaer, New York*. Ferric orthophosphate has been widely used as a source of iron in nutrition, although very little information has been reported on its biological utilization. It seemed particularly important, therefore, to conduct further studies on it in comparison with a recognized, highly assimilable iron compound. Accordingly, the biological availabilities of the iron in ferrous sulfate and ferric orthophosphate were compared on the basis of hemoglobin regeneration in rats made anemic from iron deficiency. A secondary comparison with ferric chloride was also made. Multiple levels of iron enrichment were used to permit comparison of dosage response curves. The food mixtures contained the added iron in the following concentrations: ferrous sulfate iron, 13, 86, 172, and 344 µg per gram; ferric orthophosphate iron, 69, 172, 344, and 1076 µg per gram; and ferric chloride iron, 86 and 172 µg per gram.

Under the conditions of these experiments, iron in the form of ferrous sulfate was approximately 4 times as available as ferric orthophosphate iron when both compounds were tested at 4 widely spaced levels. In the secondary comparison at 2 levels, iron given as ferric chloride was equal in biological availability to the highly effective ferrous sulfate iron, and therefore was also approximately 4 times as available as iron given as ferric orthophosphate.

Molded feedstuff as a source of growth factors for chicks RAYMOND BORCHERS and GEORGE L. PELTIER (introduced by C. P. Berg) *Depts. of Agricultural Chemistry and Bacteriology, Univ. of Nebraska, Lincoln*. A molded feedstuff was prepared by growing a gold *Aspergillus* species (U N F 331) on a moistened, sterilized mixture of wheat bran, cracked corn, and soybean meal. When this material was dried and fed at a 10 per cent level in a typical basal ration (containing no animal protein) to chicks, the average four-week weight was increased significantly over that of chicks fed the basal ration with 10 per cent of the sterilized

mixture not molded Supplementing the basal ration with 0.3 gram choline chloride, 0.2 mg riboflavin, 3 mg niacin, 0.4 mg pyridoxine hydrochloride, and 1 mg calcium pantothenate per 100 grams resulted in approximately the same average four-week weight as the basal ration plus the molded feedstuff Supplementing the basal ration with both the molded feedstuff and the five factors named above did not result in a further growth increase Microbiological riboflavin assay of several preparations of the molded feedstuff gave values from 3-5 mg per 100 grams

The influence of fat and carbohydrate calories on protein utilization DAVID K BOSSHARDT (by invitation), WINIFRED J PAUL (by invitation), KATHLEEN O'DOHERTY (by invitation) and RICHARD H BARNES *Dept of Biochemistry, Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pa* The influence of calorie intake on protein utilization by growing mice was determined for two protein sources with different nutritive qualities wheat gluten and casein Under conditions of *ad libitum* feeding it was noted that the calorie intake necessary for optimal utilization was greater for casein than for the poorer protein wheat gluten This observation suggested the possibility that nitrogen equilibrium could be attained with wheat gluten at a lower calorie intake than with casein

The degree of utilization of the two proteins was determined at reduced calorie intakes The protein source was fed to all animals so that the daily intake was the same as that which resulted in optimal utilization when the feeding was *ad libitum* Thus the daily intake of wheat gluten was 0.6 gram/mouse and of casein, 0.2 gram/mouse All studies were of ten days duration With each protein, two series of diets were employed In one series the daily calorie intake was varied by changing the amount of carbohydrate ingested and in the second series by changing the amount of fat ingested In each series there was only one dietary component that was varied, all other components being fed in equal amounts

The results indicated no difference in the protein sparing of fat and carbohydrate calories It was noted, however, that the calorie intake could be reduced to a point (approximately 75% of the minimum required for optimal protein utilization) where the nitrogen of the wheat gluten diets was utilized more efficiently than was that of the casein diets

Diet of the mother and brain hemorrhage in infant rats E E BROWN (by invitation), J F FUNGL (by invitation) and L R RICHARDSON *Division of Chemistry, Texas Agricultural Experiment Station, College Station, Texas* Brain hemorrhages occurred in 48 out of 97 young born to mothers which received a diet low in fat and deficient in vitamin K The basal diet was composed

of cerelese 67, casein (acid washed) 25, salt mixture 5, wood pulp 3 and was supplemented with adequate amounts of vitamins A and D, alpha tocopherol, thiamine, riboflavin, pyridoxine, pantothenic acid, niacin, choline, p aminobenzoic acid, inositol and biotin No hemorrhages occurred in a total of 298 young from mothers that received the same diet supplemented with 10 per cent of lard and 2.5 mg of vitamin K per 100 grams of diet or with lard or vitamin K separately

A total of 14 young in 4 litters were weaned from females that received the basal diet for less than 45 days When the mothers received the basal diet for a longer period none survived and 70.5 per cent had brain hemorrhages Most of the young are born dead or die within 24 hours after birth Four died between the 8th and 10th day and 5 between the 15th and 21st day These became unstable before death and dark areas on the brain were visible which proved on autopsy to be due to hemorrhages Seven of the 48 young also had hemorrhages on the back and 3 had blood in the intestines

The blood coagulation time of 5 females that had borne hemorrhagic litters and of 3 young with brain hemorrhages was normal

The effects of certain amino acids and choline on the production of polycythemia by cobalt MARY C BUCCHIERO (by invitation) and JAMES M ORTEN *Dept of Physiological Chemistry, Wayne Univ College of Medicine, Detroit* There is evidence that cysteine and, to a lesser extent, cystine and methionine decrease the toxicity of cobalt in the rat, and also that histidine decreases the toxicity of cobalt in mice and in certain microorganisms These observations raise the question of whether these amino acids may also affect the production of polycythemia by cobalt The present experiments were designed to study the effects of cysteine, methionine, and histidine on the polycythemic action of cobalt in the rat and also that of choline which has been alleged to inhibit the polycythemia produced by cobalt

Groups of 12 weanling male albino rats were fed an adequate synthetic diet One group was given cobaltous sulfate at a level of 100 mg cobalt per kilo diet A second group was administered cobalt supplemented by cysteine at two levels, 1.56 and 4.68 grams per kilo diet Third, fourth, and fifth groups received cobalt with either methionine or histidine in amounts iso molar with the higher cysteine level, or choline iso molar with the two cysteine levels An unsupplemented group served as controls Body weights and food intakes were followed weekly and hemoglobin determinations were made bi-weekly

The results demonstrate that choline had no detectable effect on the development of the polycythemia whereas cysteine showed a distinct inhibitory effect There was an attendant increase



in body weight over that of the animals given cobalt alone. Methionine, although also having a definitely beneficial effect on growth, has shown little depressing effect on the polycythemia. The studies on histidine are in progress.

**Nitrogen metabolism in college women.** DANA C. CEDERQUIST (by invitation), WILMA D. BRLWIK (by invitation), NORMA JEAN RADAR (by invitation), and MARGARET A. OLSON, *Dept. of Foods and Nutrition, School of Home Economics* and E. J. BLUNNE (by invitation), *Agricultural Exp. Station, Michigan State College, East Lansing*. Six women, 18 to 24 years of age, were maintained on weighed diets for a total of 612 days. Each subject was studied through five experimental periods: (1) self-selected diet, (2) restricted protein, (3) moderate protein, (4) high protein and (5) restricted protein intake. The 7 day menus used for the 4 controlled dietary periods were planned from foods normally consumed by college women. The intake of protein was varied by changes in the quantities of milk and meat offered. Calorie requirements were met by ad libitum allowances of pure sugar candy and fats. Each 7 day balance period was preceded by a 7 to 18 day adjustment period.

When the results of all of the nitrogen balance studies were plotted against nitrogen intake per square meter of body surface or nitrogen intake per kilogram of body weight, the estimated intake of protein at zero balance was 45 to 48 grams for a 60 kilogram woman. This estimate agrees with that reported in a study of college women on a self-selected diet (H. McKay, *et al*, *J. Nutr.* 24: 367, 1942) but is considerably in excess of that reported as the minimum protein requirement of adults (D. M. Hegsted *et al*, *J. Lab. Clin. Med.* 31: 261, 1946).

**Utilization of calcium pantothenate and biotin by lactating women.** MARGARET N. CORRELL (introduced by Icie G. Macy), *Research Lab., Children's Fund of Michigan, Detroit*. Calcium pantothenate and biotin were determined microbiologically in food samples representing diets, "as eaten," of healthy nursing mothers and in corresponding 24 hour collections of their milk and urine. The women were studied during two 5 day periods immediately following delivery and at intervals postpartum (2 to 10 months) while they were producing mature milk. Breast milk was obtained by manual expression at 4-hour intervals.

Diets provided average daily intakes of 7.97 mg of calcium pantothenate. Average daily secretion in immature milk was 1.28 mg during the first 5 days postpartum, 3.56 mg the second 5 days, 17 and 44 per cent of the intake, respectively. Mature milk averaged 1.72 mg daily, 21 per cent of average intakes for the same periods. Urine contained averages of 60 and 64 per cent of intakes during the

first and second 5 day periods postpartum, respectively, and 56 per cent of intake during mature milk secretion.

Average daily biotin intake was 86.1 micrograms, of which 57.1 micrograms, 67 per cent, was "free," or "loosely bound." Biotin in milk was extremely low for the first 5 days postpartum. Average daily secretion in immature milk during the second 5 days was 5.1 micrograms, 6 per cent of intake. Average amount in mature milk was 5.7 micrograms, 7 per cent of the corresponding intake of biotin. Urine averaged 14 and 36 per cent of intakes, respectively, during first and second 5 days of the puerperium, and 17 per cent of intakes during production of mature milk.

**Relation of carbohydrate to intestinal synthesis of biotin and hatchability in mature fowl.** W. W. CRAWFORD and J. R. COUCH (introduced by C. A. Iveljhem), *Depts. Poultry Husbandry and Biochemistry, Univ. of Wisconsin, Madison*. Pullets fed a synthetic diet (B31) with sucrose as the carbohydrate maintained a high level of egg production during a ten week period, hatchability of the eggs decreased to zero by the end of the third week and remained at this level. An identical diet (B32) except for the substitution of dextrin for sucrose supported normal egg production, and hatchability ranged from 60-90 per cent. Diet B31 plus 200 micrograms of biotin per kilogram supported hatchability equal to that of a practical control ration.

The biotin content (determined by microbiological assay) of the yolks of eggs from pullets fed Diet B31 decreased from 510 to 48, while that of the whites decreased from 65 to less than 15 millimicrograms per gram by the end of the third week of the experiment. Biotin analyses of eggs from pullets fed Diet B32 showed that the yolks had decreased from 515 to 343 while the whites decreased from 88 to 24 millimicrograms of biotin per gram at the end of the third week. Diet B31 plus 200 micrograms of biotin per kilogram maintained a level of this vitamin in the eggs equivalent to that of eggs from pullets fed the practical ration.

Substitution of part of the sucrose in Diet B31 by lactose or dextrin resulted in a marked reduction in egg production.

The increased hatchability and the increased biotin content of eggs from pullets fed dextrin in contrast to those fed sucrose suggests that dextrin favors intestinal synthesis of biotin in the mature fowl.

**Medical nutritional aspects of troops allowed free choice of any quantity of any item in a packaged ration.** L. V. CROWLEY (by invitation), R. E. JOHNSON and G. V. ANDERSON (by invitation), *U. S. Army Medical Nutrition Lab., 1849 West Pershing Road, Chicago 9, Illinois*. A field test of packaged rations was conducted in the Rocky

Mountains in the summer of 1946 during which troops underwent a course of training in mountain warfare while living in a bivouac area under constant experimental supervision. One company of 120 men for control purposes, subsisted on an abundant garrison ration, and another for one month was allowed unlimited choice of any quantity of any item in a packaged ration that under ordinary operational conditions offers a soldier in one day three cans of meat product, one can of fruit, one can of bread, soda crackers, a cookie, a cereal disc, jam, fudge, synthetic fruit beverages, cocoa, coffee and sugar.

Both companies in thirty days gained about 3 pounds per man in body weight on observed intakes of 5000 (controls) and 4500 (free choice) Calories per man per day. No significant average differences were detectable between the companies in physical examination, physical fitness tests, military efficiency, hemoglobin, serum protein or urinary excretion of thiamine, riboflavin and ascorbic acid. The average daily nutrient intake of the free choice company was above NRC recommended allowances in all respects.

It is concluded that normal appetite leads troops to the selection of a good diet provided there is no economic limitation and provided that a wide variety of acceptable ordinary foods is available in abundance.

Some effects of refeeding male albino rats after caloric restriction. ESTHER D'ACOSTA (by invitation), R. E. JOHNSON and G. H. BERRYMAN (by invitation). *U S Army, Medical Nutrition Laby, 1849 West Pershing Road, Chicago 9, Illinois*. During 10 weeks of caloric restriction, 76 rats fed 38 Calories per day of a diet containing 20% protein lost 18.5% in weight. Seventy six rats fed the second type of diet or 32 Calories per day of a diet containing 8.5% protein, lost 30.4% in weight. Twelve controls gained 22.3% in weight.

After the period of restriction the rats were fed *ad libitum* either a high fat (28%), high carbohydrate (77%), high protein (40%) or free choice diet. At intervals groups were killed to determine the effect of these diets on the specific gravity and on the fat and water content of the total animal and different organs.

After one week of refeeding rats fed high fat regained 29%, rats fed high carbohydrate, 18 to 23%, high protein, 15 to 18% and free choice animals 21 to 24% in weight. The greatest gains in fat occurred in rats fed a high fat diet and the greatest of these gains occurred in the skin. Water content varied roughly inversely with fat content and rats fed a high carbohydrate diet showed the highest relative water content.

After four weeks refeeding rats on high fat gained 46 to 47% on high carbohydrate 36 to 41%,

on high protein 24 to 48% and on free choice 36 to 46% in weight.

Specific gravities roughly followed the picture of the rat's fat content, being lowest in the rats fed high fat and highest in the depleted group.

Synthesis of B vitamins by the rat. FLOYD S. DAFT. *National Inst of Health*. Weanling rats given a diet containing 4% of casein as the sole source of protein became anemic, leucopenic and granulocytopenic. Treatment of such animals with pteroylglutamic acid or with 15 unit liver extract was followed by increases in the levels of circulating white cells while treatment with p-aminobenzoic acid was without demonstrable effect. The activity of the liver extract could not be explained on the basis of its pteroylglutamic acid content and may possibly have been due, therefore, to the antipernicious anemia substance which it contained.

Treatment of deficient rats with a high casein diet or with the ten essential amino acids resulted in increased food consumption, an increased rate of growth, and in a slow but complete correction of the blood dyscrasias. This correction could be hastened by the inclusion of p-aminobenzoic acid in the diet.

From these data it appears probable that the rat is able under suitable conditions to synthesize pteroylglutamic acid, or a factor in purified liver extract, or both. The apparent dependence of these processes on an adequate supply of protein or amino acids suggests that essential amino acids may be spared when adequate amounts of these vitamins are administered. The possible bearing of these results on the problem of interchangeability of vitamins will be discussed.

The vitamin M group and gastrointestinal absorption in the human. WILLIAM J. DARBY, EDGAR JONES (by invitation), HENRY F. WARDEN (by invitation), and MARGARET M. KASER (by invitation). *Depts of Medicine and of Biochemistry, Vanderbilt Univ. School of Medicine, Nashville, Tennessee*. The response of patients in six relapses of sprue has been followed after therapy with the vitamin M group (pteroylglutamates) only. Satisfactory hematologic remissions have been accompanied by clinical evidences of improved gastrointestinal absorption, by relief of glossitis, cessation of diarrhea, and by chemical changes interpreted as indicating improved absorption of glucose and of fat soluble substances from the alimentary tract. These chemical evidences are (1) a rapid return toward normal of the flat glucose tolerance curves characteristic of sprue, (2) a more gradual return toward normal of the vitamin A and tocopherol tolerance curves, (3) a rise in serum carotene and tocopherol levels, (4) a decrease in the prothrombin time. Less extensive data indicate that the stool fat content decreases and that the abnormal gastrointestinal pattern on X ray returns slowly toward

a normal pattern. The evidence is compatible with the concept that the vitamin M group is of importance in maintaining normal gastrointestinal absorption. The mechanism of this action is being studied. [Supported by grants from the International Health Division of The Rockefeller Foundation, the Nutrition Foundation, Inc., the Tennessee Department of Public Health, and the National Vitamin Foundation.]

Ascorbic acid in strawberries as measured by blood plasma of women following a test meal. BETTY JEAN EINBECKER (by invitation), LOIS JACKSON (by invitation), PAULINE PAUL (by invitation) and MARGARET A. OHLSON, *Dept. of Food and Nutrition, School of Home Economics, Michigan State College, East Lansing*. The apparent total ascorbic acid content of frozen strawberries (Roe and Oesterling, 1944) increases after a three months storage period and gradually falls. The reduced ascorbic acid (Loeffler and Pouting, 1942) is consistently lower than the total ascorbic acid and follows no specific trend for the first six months of storage. Preliminary chemical investigation did not explain the increase in apparent total ascorbic acid. Therefore, the plasma ascorbic acid concentrations (Farmer and Abt, 1936) of five young women were tested at 0,  $\frac{1}{2}$ , 1,  $1\frac{1}{2}$ , 2, and 3 hours after a basic breakfast of buttered whole wheat toast and black coffee supplemented with (1) no supplement, (2) 150 grams unsweetened frozen strawberries, (3) crystalline ascorbic acid equivalent to the amount of reduced ascorbic acid provided by the strawberries, (4) crystalline ascorbic acid equivalent to the amount of apparent total ascorbic acid provided by the strawberries.

The increases in plasma ascorbic acid obtained after ingestion of the strawberries were comparable to those obtained when crystalline ascorbic acid was taken in amounts equivalent to the reduced ascorbic acid in the strawberries. Increases obtained when crystalline ascorbic acid was taken in amounts equivalent to the apparent total ascorbic acid were greater than those obtained after the ingestion of strawberries. Urinary excretion of ascorbic acid during the 3 hours period did not account for the differences in plasma ascorbic acid. The difference between the reduced ascorbic acid and apparent total ascorbic acid of strawberries is not measurable in the plasma within 3 hours.

Utilization by human subjects of crystalline ascorbic acid and of ascorbic acid from grapefruit. KATHERINE JOHNSTONE ELLIOTT (by invitation) and CECILIA SCHUCK, *Nutrition Lab., School of Home Economics, Purdue Univ., Lafayette, Indiana*. Eight women and one man ranging in ages from 19 to 27 years served as subjects. Preceding the administration of the crystalline ascorbic acid and the grapefruit the subjects, while consuming their regular diets, were given 250 mg. daily of

ascorbic acid in tablet form for a three-day period to bring them to a state of saturation.

A basal diet containing 29 to 39 mg. ascorbic acid was administered to the subjects during each of two three day test periods. This diet was supplemented with 75 mg. crystalline ascorbic acid during the first test period and with freshly sectioned grapefruit containing approximately the same amount of ascorbic acid during the second period.

Urinary excretion of ascorbic acid was determined daily for all subjects and blood levels were determined for three of the subjects at the end of each test period. The blood levels ranged from 1.06 to 1.47 mg. per 100 ml.

The 2,4-dinitrophenylhydrazine method for "total" ascorbic acid (J. Biol. Chem. 147:399, 1943 and J. Biol. Chem. 152:511, 1944) with readings in an Evelyn photoelectric colorimeter was used to determine the ascorbic acid of the basal diet, the grapefruit supplements and the blood and urine.

The ascorbic acid not excreted was assumed to be utilized by the body. Utilization figures were calculated as the per cent of total intake retained. The results showed approximately equal utilization of the crystalline ascorbic acid and of that obtained from the grapefruit. [Aided by a grant from the Purdue Research Foundation.]

The antivitamin B<sub>6</sub> activity of desoxypyridoxine in the rat. GLADYS A. EMLERSON, *Merck Inst. for Therapeutic Research, Rahway, N. J.* An analog of vitamin B<sub>6</sub>, desoxypyridoxine, was reported by Ott to act as a powerful antagonist of pyridoxine in the chick. Two moles of desoxypyridoxine counteracted 1 mole of pyridoxine when suboptimal or optimal (but not excess) pyridoxine was administered. When desoxypyridoxine was fed to weanling rats as an adjunct to a purified diet deficient in vitamin B<sub>6</sub> and to the same ration supplemented with the quantity of pyridoxine present in a stock diet (3.4 micrograms/gram), the time required for the production of acrodynia in the deficient group was materially decreased and the signs of depletion were aggravated. The dermatitis was noted when the ratio of desoxypyridoxine to pyridoxine was 50:1 with the animals receiving the purified diet, with the stock ration the ratio was 175:1. The discrepancy between the results obtained with purified and stock diets of like pyridoxine content could not be explained by the presence of pyridoxal and pyridoxamine in the latter diet as these compounds were likewise counteracted by desoxypyridoxine. The effect of desoxypyridoxine in the production of pyridoxine deficiency was also studied in adult rats previously maintained on a stock diet. During the 4 month test period the animals receiving the pyridoxine deficient ration alone were indistinguishable from normal animals. Rats receiving the pyridoxine deficient diet con-

taining 0.5 mg % desoxyypyridoxine showed aerodynia at an average of 55 days and the growth rate was depressed.

Relative effectiveness of choline, methionine, betaine, casein and egg albumen in preventing kidney hemorrhage. R. W. ENGEL (introduced by W. D. Salmon) *Laby of Animal Nutrition, Alabama Polytechnic Inst., Auburn*. The relative effectiveness of choline Cl, dl-methionine, betaine HCl, casein and egg albumen as methyl donors for the prevention of hemorrhagic kidneys in choline deficiency was studied. The results given represent comparisons between litter mate weanling rats.

A diet with varying amounts of added crystalline dl-methionine was compared with the same diet containing 0.6% choline Cl, a level which resulted in kidney hemorrhages in approximately 50% of the animals. The same magnitude of kidney damage was observed when the diet contained from 275 to 300% dl-methionine, a level about 50% greater than the theoretical amount required based on methyl equivalents.

Naturally occurring methionine in casein or egg albumen was less effective than crystalline dl-methionine. Thus, increasing the casein in the diet by 10%, which increased the methionine content 325%, resulted in a 100% incidence of kidney hemorrhage compared with a 58% incidence in litter mate rats receiving the same diet containing 325% crystalline dl-methionine. Likewise, the addition of 9% egg albumen, which increased the dietary methionine 450%, was less effective than 325% crystalline dl-methionine. The kidney hemorrhage incidences were 87 and 50% respectively.

A diet containing 2 different levels of betaine HCl (130 and 195%) was compared with a 0.4% dietary level of choline Cl. The results indicate that, in methyl equivalents, the betaine HCl had only  $\frac{1}{4}$  to  $\frac{1}{3}$  the potency of choline Cl in preventing kidney hemorrhage.

Food habits and preferences of two groups of Iowa people. ERCEL EPPRIGHT (by invitation), ROBERT McMILLAN (by invitation) and PEARL SWANSON. *The Nutrition Laby, The Foods and Nutrition Section, Iowa Agricultural Experiment Station, Iowa State College, Ames*. A statistically valid picture of the food habits and preferences of 17, 18, and 19 year old boys and girls of Iowa, and of 46 to 58 year-old adults is being obtained. The master sample for the state of Iowa prepared by the Statistical Laboratory of the Iowa State College was used for setting up the study. The sampling rate was such as to yield an estimated 1300 eligible respondents, distributed according to a predetermined plan among open country, rural, and urban places. Approximately 900 schedules have been completed.

Data obtained from four areas have been partially analyzed. They show the predominance of a diet

of meat, bread, potatoes, coffee, and sweets. Variety is limited, particularly in the case of vegetables and fruits. Only 50 per cent of the daily menus included milk. There was little difference in the food selection for dinner and supper, and not much evidence of application of meal planning principles.

The familiarity of the respondents with the nation wide list of foods included in the schedule will be studied together with the "food likes" and "dislikes," and reasons for the attitude. Preferred menus and methods of preparation may be compared with the actual.

Correlations will be made between attitudes toward food and a variety of factors, as age, sex, place of residence, socio economic level, certain household facilities, and racial background.

Availability of riboflavin from food sources as judged by urinary excretion of the vitamin. G. J. FVERSON, E. K. WHEELER, and H. J. WALKER (introduced by Pearl Swanson). *Iowa State College*. Eight women subjects who consumed the same mixed diet providing 2.5 milligrams of riboflavin daily for a twelve day period excreted fairly constant quantities of riboflavin in the urine. Administration of 2 milligrams of riboflavin by retention enema on the morning of the eleventh day of this period produced no significant change in the urinary excretion of the vitamin. These eight women served as subjects during four subsequent studies designed to compare the availability of riboflavin of ice cream, almonds, and fresh frozen peas with that of a solution of the pure vitamin.

Availability was measured by comparing the increment in riboflavin excretion following supplementation of the basal diet with 1 milligram of riboflavin from each food source. Since the weight of test food needed to furnish 1 milligram of riboflavin added varying amounts of carbohydrates, protein, and fat to the basal diet, the total food consumption of these nutrients was kept the same throughout all studies by including riboflavin free sources of dextrose, casein, and butter in the original menu and then deducting the necessary quantity of each substance when fat, protein, and carbohydrate were furnished in the test food.

As daily variation in the urinary excretion of riboflavin was observed to be small for these eight subjects, a three day experimental period has been used in judging availability of the vitamin. The data indicate that there is a significant difference in the availability of the riboflavin found in certain food sources.

Studies on the vitamin requirements of highly inbred strains of mice. riboflavin and pantothenic acid. PAUL F. FENTON (by invitation) and GEORGE R. COWGILL. *Iale Nutrition Laby, Dept of Physiological Chemistry, Yale University*. Male mice of the C<sub>57</sub> strain, weaned when 21 days old

were placed for one week on purified diets from which riboflavin had been omitted. After this depletion period the animals were fed diets of the same composition but containing different amounts of riboflavin. The animals were weighed daily (with few exceptions).  $C_{57}$  strain mice maintained on the "riboflavin-free" diet (actually containing 0.3 micrograms per gram diet) grew very slowly for about three weeks. The first animal died after 36 days on the diet while one mouse lived for 12 weeks. The inclusion of 4 micrograms of riboflavin per gram of diet resulted in growth of the  $C_{57}$  mouse equal to that observed with higher levels of riboflavin. Red and white cell counts, hemoglobin determinations, and riboflavin assays of muscles and livers were carried out. The pantothenic acid requirement of mice was investigated in a similar manner. Maximal growth of the  $C_{57}$  mice under these conditions was obtained with a diet containing 6 micrograms of pantothenic acid per gram. However, even at this level of intake achromotrichia and alopecia were observed. With an intake of 30 micrograms per gram only slight graying was observed in some animals during the period of most rapid growth. Male mice of the A and  $C_{3}H$  strains were studied in similar manner.

Observations on the pteroylglutamic acid content of the tissues of chickens. A. L. FRANKLIN (by invitation), E. L. R. STOKSTAD and T. H. JUKES, *Lederle Labs, Division, American Cyanamid Company, Pearl River, New York*. Various tissues have been observed to contain enzyme systems which liberate pteroylglutamic acid as the free vitamin from its microbiologically-inactive conjugated form. Attempts were made in the present investigation to inactivate the enzyme system by heat so that the pteroylglutamic acid conjugate originally present in the tissues could be measured. Chicks on purified diets with and without supplementation with pteroylglutamic acid were used. At 3 to 4 weeks, the liver tissue of the chicks was found to contain from 0.7 to 1.9 micrograms of free pteroylglutamic acid per gram. After autolysis, the value increased to from 8.0 to 12.1 micrograms. When the tissue was treated with chicken pancreas as a source of "conjugase," the value ranged from 11.3 to 14.0 micrograms per gram. Lower values were found for fresh muscle and heart tissue than for liver, but marked increases were also produced in muscle and heart tissue by autolysis or by treatment with conjugase. After 7 weeks depletion on the basal diet, the free and conjugated pteroylglutamic acid content of the liver muscle and heart tissues of a chick were found to be lowered to only one-tenth of the values of a corresponding group of chicks at 4 weeks. The results indicated that the major part of the pteroylglutamic acid content of the tissues examined was present in the conjugated form.

The blood lactate-pyruvate relationship in various physiologic and pathologic states. GRACE A. GOIDSWORTHY, *Nutrition Research Lab., Dept. of Medicine, Tulane Univ. School of Medicine*. The relationship of lactic acid to pyruvic acid in the blood was studied in 29 normal persons and in 41 hospitalized patients. The mean lactate-pyruvate ratio in the normal persons was  $9.27 \pm 1.66$  in the basal state,  $9.43 \pm 1.97$  after the administration of glucose,  $10.04 \pm 3.13$  after a meal and slight activity, and  $18.26 \pm 3.16$  after strenuous exercise. A ratio similar to exercise was obtained following electric shock therapy. The lactate-pyruvate relationship can be expressed graphically or by formula for a given physiologic state. These findings confirm those of Stotz and Bessey but differ in the mathematical relationships observed.

The mean lactate-pyruvate ratio in the basal state was 9.68 in 19 patients with various afebrile diseases, 6.72 in six patients with clinical evidence of thiamine deficiency, 7.94 in seven patients with signs of riboflavin and niacin deficiency and 7.84 in nine patients with heart disease. A lactate-pyruvate ratio of less than 7.0 was found in eleven persons, one presumably normal, one with contact dermatitis, five with vitamin B complex deficiency and four with heart disease. After treatment with thiamine the lactate-pyruvate ratio was normal in the six patients in whom it was measured, four with cardiac and two with deficiency disease. Whether or not the low ratio in heart disease was due to thiamine deficiency requires further study. Determination of the lactate-pyruvate ratio may be of assistance in evaluating the status of human thiamine nutrition.

Antithiamine activity of bracken fern. J. R. HAG, P. H. WESWIG (by invitation) and ANNA MAY FREED (by invitation), *Oregon State College, Corvallis, Oregon*. "Fern poisoning" in livestock has for many years been associated with grazing in areas where bracken fern (*Pteris aquilina*) occurs. Attempts to determine the etiology of this disorder have been conspicuously unsuccessful. Our studies with rats were begun in 1945 with a lot of fern obtained from an area where a serious outbreak of fern poisoning was taking place. This, and subsequent lots of fern, 10 in all, from five different areas, and seasons ranging from May to October, were air-dried at room temperature and incorporated into normal rations at levels from 15 to 40% of the total ration.

Rats fed such rations developed marked symptoms of thiamine deficiency including anorexia, emaciation and polyneuritis, terminating in death. The daily administration of 0.5 mg. thiamine per os, with few exceptions, resulted in spectacular recovery. Rats have continued to make normal gains for as much as 15 weeks while receiving fern rations supplemented with thiamine.

The causative agent is essentially insoluble in ethyl ether, petroleum ether, acetone and ethyl alcohol. In the air-dried state it possesses considerable heat stability as evidenced by heating overnight at 105°C. Boiling in water for 30 minutes and subsequent drying on the stock ration largely or entirely inactivates the factor. In addition to its isolation and identification, our observations raise two important questions:

1. How widely is antithiamine activity distributed among plant materials?
2. What are the implications of our findings with respect to "fern poisoning" and to ruminant nutrition?

Ocular changes resulting from nutritional deficiencies in the rat. W. KNOWLTON HALL (by invitation), V. P. SIDENSTRICKER, LESTER L. BOWLES (by invitation), LANE ALLEN (by invitation), J. L. BERG (by invitation) and E. R. PUND (by invitation). *Depts. of Biochemistry, Medicine, Micro-anatomy, Gross Anatomy and Pathology, Univ. of Georgia School of Medicine, Augusta, Georgia.* Photographs will be shown of corneal preparations in which the blood vessels in the limbic area and capillaries of the cornea have been injected with India ink. These photographs will show the type and extent of corneal vascularization resulting from deficiencies of protein, the indispensable amino acids, riboflavin, pantothenic acid, pyridoxin and vitamin A. The histological changes in the cornea due to methionine deficiency will also be illustrated.

Photographs of cataracts which appeared in rats fed a diet deficient in histidine will be shown with similar photographs of cataracts due to other causes. [This investigation was aided by grants from Merck and Co., The John and Mary R. Markle Foundation and the U. S. Public Health Service.]

Influence of thyroid activity on liver lipids in choline and cystine deficiency. PHILIP HANDLER. *Dept. of Biochemistry, Duke Univ. School of Medicine, Durham.* V. C. Young rats, initial weight 100 grams, were fed a basal ration of casein 10, sucrose 58, cotton oil 10, lard 15, salts 3, cod liver oil 3, and cholesterol 0.5, adequately supplemented with a mixture of crystalline B vitamins for three weeks. They were sacrificed by carotid exsanguination and the liver lipids determined by standard procedures. The various supplements and the results are given in the following table. Each value is the mean of a group of 8 rats.

The diminished phospholipid concentrations merely represent dilution by the other lipids. Increased thyroid activity decreased the deposition of neutral fat and of cholesterol. Essentially similar changes occurred in cystine deficiency. Thiouracil, by depressing thyroid activity, markedly increased cholesterol deposition and to a lesser degree neutral

Supplement	Liver lipids		
	Total	Cholesterol	Phospholipids
	%	%	%
Choline + Cystine	7.1	0.35	2.52
Choline + Cystine + Thyroid	4.6	0.19	2.54
Choline + Cystine + Thiouracil	11.0	1.03	2.56
Cystine	23.5	0.77	1.68
Cystine + Thyroid	17.8	0.39	1.89
Cystine + Thiouracil	30.5	1.23	1.54
None	16.1	0.41	2.04
Thyroid	9.7	0.26	2.31
Thiouracil	21.3	0.78	1.76

fat as well. [This investigation was supported by grant from the Nutrition Foundation, Inc.]

Dental caries in the rat (*Mus norvegicus*). JULIA O. HOLMES, L. R. PARKINSON (by invitation), ANNE W. WERTZ (by invitation), BEULA V. McKEY (by invitation), and LOIS BROW (by invitation). *Agricultural Experiment Station, School of Home Economics, Massachusetts State College, Amherst.* This study on tooth decay involves the feeding of over 70 different rations or supplements to 850 rats. The Cox system of rating dental caries has been used. On the Hoppert, Webber and Canniff ration occlusal caries was advanced at 14 weeks and was not influenced by any of the known vitamins or by butterfat, yeast, vitab, beef muscle or liver, or L-tryptophane. The cooking of the corn, the addition of 16% casein, and a reduction in particle size decreased decay by 64, 33 and 23%, respectively, below that observed in litter mate controls.

With synthetic rations, mild occlusal caries was observed at 14 weeks when the carbohydrate was glucose or sucrose, but not starch.

Of 5 fractions of corn fed singly in connection with starch rations the only one which induced occlusal caries in 100% of the rats was a corn gluten concentrate containing approximately 50% protein.

On the hypothesis that the caries inducing or -inhibiting properties of a ration are related to the type of compounds synthesized by the intestinal bacteria, substances have been fed in an attempt to modify the intestinal flora.

Another approach has been to feed substances which alter the metabolic activity of the body.

The feeding of sulfasuxidine, D-1 valine, and pulsatilla, substances with antibiotic properties, and D-1 tryptophane did not alter the incidence of decay. Raw tomato caused marked erosion of dentin on occlusal surface of cusps.

The data will be presented in terms of occlusal and fissure caries.

Unknown dietary factor or factors needed by lactating cows depleted on legume hay alone. C. F.

HUFFMAN and C W DUNCAN (by invitation) *Michigan State College* The cows used in this study were fed legume hay alone starting at calving time. Efficient use was made of the total digestible nutrients in the hay during the first 6 to 10 weeks when milk production dropped rapidly to a low level before leveling off. The cows were considered depleted of the unknown milk stimulating factors at this time. Legume hay as a sole ration for dairy cows is deficient in an unknown factor or factors necessary for maximum lactation. The deficiency is not due to a lack of digestible energy because corn sugar or corn starch added to the ration of depleted cows did not result in an increase in milk production. Milk production increased when corn replaced the sugar or the starch in the ration. Total protein intake was always adequate.

A mixture supply 25 mg thiamine, 10 mg riboflavin, 800 mg nicotinic acid, 400 mg pantothenic acid, 200 mg inositol, 400 mg p-aminobenzoic acid, 10 grams cystine and 4 grams choline daily as a supplement to hay alone failed to increase milk production.

When one pound of brewers dried yeast or one pound each of yeast and pig liver meal per day replaced an equal amount of total digestible nutrients in hay, no appreciable increase in milk yield occurred.

Partial replacement of total digestible nutrients of the hay with low fat feeds, beet pulp and corn gluten meal, resulted in a marked increase in milk production, which indicates that total fat is not the first deficiency of a ration of legume hay alone.

**Production of niacin deficiency in rats** JAMES M HUNDLEY (introduced by F S Daft) *Division of Physiology, National Inst of Health, Bethesda, Maryland* Rats growing on a purified ration containing 9 or 12% casein plus 15% 1(-)-cystine, with sucrose as the carbohydrate, showed significant improvement in weight gain when 2 mg % niacin or 200 to 400 mg % dl tryptophane was added to the ration. Niacin had no effect in rats receiving 20% or more casein.

The urinary N<sup>1</sup>-methylnicotinamide excretion of the 9 and 12% rats was 29 and 45  $\gamma$ /100 gram body wt/day respectively, as compared to 154  $\gamma$  for rats on 20% casein. The addition of 2 mg % niacin to the diet caused the excretion by the 9 and 12% animals to rise to 204 and 158  $\gamma$  respectively, but caused no significant change with 20% or more casein. 400 mg % dl tryptophane added to the diet increased the excretion of the 12% rats from 45 to 1142  $\gamma$ .

Assays of liver and muscle showed markedly depressed niacin levels in the 9 and 12% rats which were brought to normal by supplemental niacin.

Other diets made with 9% casein plus varying amounts of tryptophane deficient protein such as gelatin, acid hydrolyzed or oxidized casein, or pure

amino acids caused a growth depression interchangeably corrected by either niacin or tryptophane.

These data were interpreted as indicating that tryptophane is the dietary precursor for niacin synthesis in the rat. Since these diets were probably free of any "toxic" factors such as have been reported in corn, it seems clear that niacin deficiency can develop where the only etiologic agent is an amino acid imbalance with tryptophane chiefly limiting.

**Interpretation of the basal metabolic rate of children of unusual body build** ALBERTA ILIFF (by invitation) and ROBERT C LEWIS *Child Research Council and Dept of Biochemistry, Univ of Colorado School of Medicine* Since widely divergent results for the basal metabolic rate, expressed as percentage deviation from the standard, are obtained for children of unusual body build when different methods of reference are used, a study has been made to determine the relative predictive value of six of these methods. The standards that were studied are calories per hour per square meter, calories per hour per kilogram and calories per hour per centimeter, each referred to age, and calories per hour referred to weight, height and surface area, respectively. The data used for this purpose are the results of 565 determinations of basal metabolism obtained on children between 2 and 15 years of age, inclusive, whose weight or height, or both weight and height, fell above the ninetieth percentile or below the tenth percentile of the children of similar age on whom the standards of the Child Research Council were established. The analysis shows that only with calories per hour per square meter referred to age, calories per hour referred to weight, and calories per hour referred to surface area are the great majority of tests within  $\pm 15$  per cent of the standard for all extremes of body build observed in our series of children. Whether the child is small or large, short or tall, thin or obese, a single criterion suffices to give a reliable estimate of his basal metabolism with any one of these three standards.

**Vitamin deficiencies in the calf** B CONNOR JOHNSON (by invitation), H H MITCHELL, T S HAMILTON and W B NEVENS (by invitation) *Division of Animal Nutrition and Dept of Dairy Husbandry, Univ of Illinois, Urbana* A "synthetic ration" consisting of casein, cerelese, lard, minerals, and vitamins, prepared to simulate cow's milk, has been developed for the new-born calf. New-born calves were raised successfully on this ration for a period of twelve to sixteen weeks irrespective of whether they received colostrum.

With this synthetic ration calves receiving colostrum did not require ascorbic acid. Riboflavin and biotin deficiencies were produced in the calf and the syndromes have been described.



Nicotinic acid was not required by the calf on this ration which contained 30 per cent casein (dry basis), even when colostrum was not provided. However, the urinary excretion of nicotinic acid and of an acid hydrolyzable precursor could be increased by the administration of tryptophane, suggesting that nicotinic acid may be required on a lower protein ration.

Two other vitamins were studied—thiamin and pantothenic acid. Both have been shown to be required by the new-born calf. The symptoms of the thiamin deficiency include anorexia, diarrhea, weakness, poor coordination, and muscular twitching. These symptoms were alleviated rapidly by the injection of thiamin. On the thiamin-free diet the thiamin excretion dropped to a very low value within two weeks.

The pantothenic acid deficiency was characterized by diarrhea, cessation of growth, and weakness of the legs with inability to stand. The calves responded to pantothenic acid dosage. Again, as with riboflavin, biotin and thiamin deficiencies, the urinary level of pantothenic acid decreased rapidly to a low level on the pantothenic acid-free ration.

**Effect of feeding succinylsulfathiazole to rats on a diet low in choline.** JAMES H. JONES, *Dept. of Physiological Chemistry, School of Medicine, Univ. of Pennsylvania, Philadelphia*. To study the problem of the possible synthesis of choline by intestinal bacteria, rats at age intervals of 5 days (25 to 50 days) were placed on a synthetic diet low in choline and containing 18% fibrin. Each age group was divided into two subgroups, one of which received the basal diet and the other the same diet plus 1% of succinylsulfathiazole. After one week the animals were killed, the kidneys examined and weighed, and the livers analyzed for total fatty acids. As the starting age of the animals increased, the severity and incidence of the hemorrhagic condition decreased, but was observed in all groups. There was no appreciable difference between the two subgroups in respect to the kidneys at any age level. There was a slight but consistently larger percentage of fatty acids in the livers of the animals receiving the sulfa drug (statistically significant in only two groups).

In other experiments 5% of the succinylsulfathiazole was used, and it was given for a period before the initiation of the choline free diet either as part of the stock diet or of a synthetic diet containing choline. The succinylsulfathiazole decreased the rate of growth on the synthetic diet both with and without choline but not on the stock diet. Pteroylglutamic acid did not materially increase growth. Again there was no definite difference in respect to kidney damage and fatty livers between the animals on the basal diet and those receiving the drug.

**Effects of low potassium and low lysine diets on poliomyelitis in mice.** JAMES H. JONES, CLAIRE FOSTER (by invitation), WERNER HEYLE (by invitation) and DOROTHY ALEXANDER (by invitation). *Depts. of Physiological Chemistry and Pediatrics, Univ. of Pennsylvania, and Children's Hospital of Philadelphia, Philadelphia, Pa.* The effect of a deficiency of potassium on the response of mice to the murine-adapted Lansing strain of poliomyelitis virus was studied in two experiments. In each experiment two groups of animals were given the deficient diet and two the same diet containing ample potassium. After the deficiency had developed one group on each diet was inoculated with virus and the other with a suspension of uninfected brain. The mice on the potassium-low diet were definitely deficient in both experiments as indicated by failure of growth and a few deaths in the deficient groups not receiving virus. A total of 316 animals was used in the two experiments. There was no evidence that the deficiency had any effect on the progress of the disease. Considering the two experiments together, on the 21st day after inoculation the percentages of deaths of the inoculated animals on the complete and on the deficient diets were identical (81%). At no time during the post inoculation period of 28 days was there any appreciable difference in death rate or in incidence of paralysis between these two groups.

293 mice were used in two lysine-deficient experiments conducted as described above. On the 21st day after administering the virus the percentages of deaths of the inoculated animals on the complete and deficient diets were 88 and 80 respectively. Again the death rates and incidence of paralysis were approximately the same in these two groups throughout the 28 day period following inoculation.

**Preliminary observations on ascorbic acid and the vitamin B-complex during pregnancy and lactation.** MARGARET M. KASER (by invitation), PAULINE JONES (by invitation), G. SYDNEY MCCLELLAN (by invitation), RICHARD O. CANNON (by invitation), and WILLIAM J. DARBY. *Depts. of Biochemistry, Obstetrics, and Medicine*. Once each trimester and six weeks postpartum serum ascorbic acid and the urinary excretion of thiamine, riboflavin and N-methylnicotinamide for a two hour period following test doses of 5 mg. thiamine, 5 mg. riboflavin and 50 mg. nicotinamide were determined on 156 subjects observed by the Vanderbilt Cooperative Study of Maternal and Infant Nutrition. Sixteen of the subjects came to the clinic in the first trimester of pregnancy, but laboratory examinations were done on 100 or more women in the second and third trimesters and at the postpartum visit.

No statistically significant differences were found between the observations in the first and second trimesters except for the excretion of N-methyl-

nicotinamide, the means of which increased progressively for the three trimesters from 7.28 to 12.92 and fell to 6.44 mg postpartum. The corresponding means for thiamine excretion were 0.188, 0.164, 0.113, and 0.129 mg, the only significant difference of which was between the second and third trimesters. The mean excretions for riboflavin were 0.549, 0.740, 0.521 mg for the three trimesters with the latter difference a significant one. After delivery a level of 0.162 mg was found. During pregnancy the mean levels of serum ascorbic acid varied as follows: 0.576, 0.605, 0.451 mg per cent and after delivery 0.297 mg per cent.

The serum mean ascorbic acid levels of the mothers were correlated with the type of infant feeding. The means for mothers practicing breast feeding, supplemented breast feeding and artificial feeding were 0.236, 0.269, and 0.374 mg respectively. [This study was supported by grants from the Nutrition Foundation, Inc., the International Health Division of The Rockefeller Foundation, and the Tennessee Department of Public Health.]

**The Lemon color reaction for thiamine in rice**  
**MARINUS C. KIK**, *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville*. In Lemon's method<sup>1</sup> Solution A, mixture of 500 cc 10% NaOH containing 10 grams sulphuric acid, 250 cc 10% sodium bicarbonate and 250 cc 4% sodium nitrite Solution A<sup>1</sup>, 500 cc 2% sodium formaldehyde sulphonylate and solution B 500 cc 10% IICl, containing 5 cc of 40% formaldehyde. The method: 20 cc of rice extract, 5 cc of distilled water, 2.25 cc solution A<sup>1</sup>, 3.75 cc solution A and 2.25 cc solution B are placed in test tube 1. The same solutions and extracts are placed in test tube 2 without solution A<sup>1</sup>. Wait for 5 minutes. The color in test tube 2 turns darker yellow brown. The color in both tubes could be satisfactorily matched with the aid of a Hellge pocket comparator model 605, employing the color disk for nitrate nitrogen as a permanent glass color standard. The average disk readings and thiamine values (determined with the thiochrome method) follows:

	Disk reading	Thiamine (by thiochrome method)
Rough rice	020	3.45
Brown rice	017	3.30
First break	010	1.42
Second break	007	1.15
White (head) rice	002	1.00

This method might find application in rice mills for a quick determination of thiamine in rice milling products of the same rice variety, and in

its present form, is more qualitative than quantitative.

**Photo electric control of rice milling**  
**MARINUS C. KIK and CLARENCE G. LEONARD** (by invitation), *Dept of Agricultural Chemistry, Univ of Arkansas, Fayetteville*. In the practice of rice milling, the miller constantly inspects *visually* the rice stream for the proper milling control. A preliminary study was made of the possibility of photo electrically detecting difference in degree of whiteness in different mill products obtained in the course of the rice milling process. Whole kernels and ground grains were placed in a small glass disk and tested for whiteness. The self made instrument, used as a reflectometer, consisted of a light bulb, photronic cell, rheostat and a microammeter, 0-300 m.a. The following readings were obtained, expressed in microamperes. White paper was set at zero.

Type of rice	Whole kernel	Ground kernel
Brown	224	70
First break	210	28
Second break	204	16
White (head) rice	200	10

Observations were also made using transmission measurements with the aid of a photo electric colorimeter. However, large variations were found due to varying orientation of the rice grains in samples of the same variety and to size of the grains of different varieties. Rapid evaluation of nutritive value of rice is obtained when these results can be correlated with content of some of the nutrients.

**Pantothenic acid deficiency as affected by diet composition**  
**W. A. KREHL** (by invitation), **ALBERTO CARVALHO** (by invitation) and **GEORGE R. COWGILL**, *Yale Nutrition Lab., Dept of Physiological Chemistry, Yale Univ*. Inasmuch as the dietary protein level may influence the rat's pantothenic acid requirement, and since dextrin seems to alter the rat's requirement for certain vitamins (i.e. niacin), a study was made to determine the combined role played by these factors in modifying the pantothenic acid requirement of the rat.

Groups of weanling male rats were fed rations containing either sucrose or dextrin with either 10, 20 or 40 per cent levels of casein plus adequate amounts of mineral salts, corn oil, and all fat soluble and B complex vitamins needed by the rat. Methionine was included except at the highest protein level.

The animals were weighed weekly and sacrificed at 6 weeks. Microbiological analyses were made for pantothenic acid, folic acid, and biotin on muscle, liver and cecal contents. The deficiency was indi-

<sup>1</sup> Not published—used by Rice Conversion Ltd., London, England.

cated by the lowered pantothenic acid content of the liver

A reduction in total white cells, with a low percentage of polymorphonuclear leukocytes was noted in deficient groups, particularly at the highest protein level

Judged by growth data, dextrin exerted a greater pantothenic acid sparing action than protein. Growth of the deficient animals, however, failed in every case to approach the controls. With groups receiving pantothenic acid, dextrin promoted growth as effectively at the 10 per cent level of casein as did sucrose with 40 per cent casein.

Although mortality was zero and symptoms of "caked whiskers" mild on the present diets, examination of the thymus and adrenal glands of all deficient groups revealed marked atrophy, and hypertrophy with hemorrhage, respectively.

Strain differences in the niacin requirement of the rat. W. A. KREHL (by invitation), ALBERTO CARVALHO (by invitation) and GEORGE R. COWGILL, *Yale Nutrition Laby, Dept of Physiological Chemistry, Yale Univ*. Previous studies on the growth promoting effect of niacin or tryptophane in corn grits rations, made with Sprague-Dawley rats, have been extended to Connecticut Agricultural Experiment Station (so called "Yale" and hereafter referred to as the "CAES" Strain) animals which in general responded like the Sprague-Dawley animals. Growth, however, on the niacin unsupplemented corn grits ration was better with the CAES Strain than with the Sprague-Dawley rats. On this diet, kynurenic acid could not replace tryptophane in effecting growth although the metabolic formation of niacin from tryptophane has been reported by others.

When the casein level of the niacin free basal ration was reduced to 9 or 10 per cent, growth of the CAES Strain was about twice that of the Sprague-Dawley animals. The administration of niacin to the Sprague-Dawley animals obliterated this difference. Furthermore, when diets contained dextrin instead of sucrose, little difference in growth was observed between these strains. Although this marked change in the niacin requirement and effectiveness of added niacin has not heretofore been observed in the Sprague-Dawley strain, the addition of a tryptophane free protein (gelatin) to the 9 per cent casein basal ration further depressed growth as previously shown.

Because of the reported growth depressing action of indole 3-acetic acid in niacin free low protein diets, both strains were given this compound at relatively high levels. No significant growth depression was observed by either strain from that on the basal diet. In addition, indole 3-propionic and indole 3-butyric acids were not harmful to the CAES Strain.

Effect of protein, vitamin, and mineral supple-

ments on blood regeneration in women donors. RUTH M. LEVERTON, and DORETTA SCHLAPHOFF (by invitation), *Nutrition Laby, College of Agriculture, Lincoln, Nebraska*. One hundred and forty six studies were made of the rate of hemoglobin, red cell, cell volume, and serum protein regeneration in women blood donors. Different supplements were given to different groups of subjects daily for six weeks following a blood donation of 500 ml as follows: 40 grams protein from food sources, 3 mg riboflavin, 75 mg iron, 1 mg copper. Controlled diets were supplemented with 25 grams protein. Different groups of subjects received different supplements daily for 5 days prior to the blood donation as follows: controlled diet which furnished 100 grams protein, 75 mg iron, 75 mg iron plus 2 mg copper. Analysis of the blood was made at weekly intervals for six weeks following the donation and the results expressed in terms of the percentage of the value at the time of donation.

All of the supplements improved the rate of hemoglobin regeneration above that of the groups on the self chosen or on the unsupplemented-controlled diet. Neither pre nor post donation supplements improved regeneration above that which occurred when the total daily protein intake was 90 grams. There appears to be a relationship between the level of protein intake and the rate of hemoglobin regeneration.

Goiter on an iodine-free diet grown by hydroponics, and excluding any goiter noxa. J. F. MCCLENDON and Wm. C. FOSTER (by invitation), *Hahnemann Medical College, Philadelphia*. In order to produce an iodine-free diet and exclude a goiter noxa we grew a diet by hydroponics in a disinfected greenhouse with disinfected water and chemicals in a goiter free region. Air was pumped through a carbon filter. Six liter mate rats from a colony that had been goiter-free for 6 years were put at weaning on the diet of 40% sunflower seed, 2.8% soy beans, 40% sucrose, 0.8% NaCl and 16.4% corn oil. Three of the rats were given water redistilled from alkali to drink and at the end of 73 days had goiters weighing 39, 42 and 41 mg per 100 grams body weight. The other 3 rats were given water containing 10 parts per million of iodine and had normal thyroids weighing 10 mg per 100 grams body weight. Since the rat cages were enclosed in a cellophane covered frame and no goitrous animals or humans had access to them we believe that so called goiter noxa is excluded. The goiters were 4 times as large as normal thyroids and twice as large as goiters in rats from a goitrous colony fed in a goiter region on a very low iodine diet raised in that region. These experiments support the thesis that iodine deficiency rather than a virus or noxa is the cause of goiter.

Nutrition of rainbow trout. BARBARA A. MC LAREN (by invitation), D. J. O'DONNELL (by

invitation) and C A ELLVHLJM *Dept of Biochemistry, Univ of Wisconsin and the Wisconsin Conservation Dept, Madison* Experiments in this and other laboratories have shown that trout cannot live on a purified diet which is adequate for the rat (vitamin C added) unless it is supplemented with fresh meat. If this ration is modified by decreasing the carbohydrate, increasing the protein, and by adding dried liver and yeast, normal growth and hemoglobin levels are obtained in yearling rainbow trout. When this diet was fed to fingerlings, they grew well and had satisfactory hemoglobin values but developed liver pathology similar to that observed with yearlings fed liver-free diets or diets containing higher levels of carbohydrates. With the addition of the B vitamins (including biotin and folic acid) the color of the livers remained normal but the enlargement was not completely counteracted. Crab meal, as a source of roughage, had the same effect as the vitamins if the liver and yeast were present. In light of these results the following purified ration was prepared: dextrin 18, casein 52, salts IV 6,  $\text{CaCO}_3$  1, crab meal 8, corn oil 13, cod liver oil 2, plus the B vitamins and ascorbic acid. Further investigations showed the level of salts and fat to be optimal and the most important constituent of the crab meal to be chitin. Deficiencies of several of the B vitamins have been produced and quantitative requirements are being determined.

The occurrence and chemistry of anasarca due to vitamin A deficiency in fattening beef cattle. LOUIS L MADSEN and I P EARLE (by invitation) *Animal Husbandry Division, Bureau of Animal Industry, U S D A, Beltsville, Md* Statistics are presented showing that over 600 beef carcasses have been condemned for generalized edema or anasarca by Federal meat inspectors during the past 6 years. Additional economic loss results from poor performance in the feed lot and deaths among fattening cattle. Anasarca developed in cattle fed either stored or new-crop yellow corn and a low-carotene roughage during long fattening periods. High quality alfalfa hay effectively cured the condition under field conditions. The major dietary error causing this deficiency disease is the use of low-carotene roughages rather than the age of the yellow corn fed.

Anasarca was readily produced experimentally by feeding a carotene deficient ration. Blood studies on field and experimental cases suggests that the two conditions are identical. The principal blood and tissue changes in affected animals were: (1) Deficiency levels of plasma vitamin A, carotene and vitamin C, (2) increase in total plasma globulin due to a marked increase in fibrinogen with smaller increases in other globulin fractions, (3) decrease in plasma albumin, (4) an increase in total plasma nitrogen with no significant change in the non-

protein nitrogen fraction, (5) little or no change in serum calcium, inorganic phosphorus and magnesium, (6) phosphatase activity of the serum was significantly reduced, (7) the ninth tenth eleventh-rib cut showed a decrease in total protein and an increase in water, particularly in the separable fat, and (8) on recovery from anasarca, a marked increase in fat resembling "steatosis" was found in many muscles.

Physiological availability of the vitamins IX influence of ascorbic acid stabilizers in fruits and vegetables. DANIEL MELNICK, MELVIN HOCHBERG (by invitation) and BERNARD L OSER *Food Research Labs, Inc, Long Island City, N Y* It has been postulated by others that fruits and vegetables contain an unknown factor, a covitamin, required for the effective utilization of ascorbic acid. Accelerated holding tests have demonstrated that the vitamin is far more stable in fruit juices (orange and enriched apple juice) than in aqueous ascorbic acid solutions adjusted to the same pH. Biological assays were conducted with human subjects to determine the availability of the ascorbic acid supplied by (a) enriched apple juice or (b) a normal adequate ration containing a variety of fruits and vegetables. The assay method is based upon the observation that under standardized conditions the urinary excretion of ascorbic acid parallels the quantity consumed. Despite the concomitant ingestion of ascorbic acid stabilizing factors, when the fruits and vegetables furnished the vitamin, the urinary excretion values were found to be no different than those obtained when the ascorbic acid was supplied in pure aqueous solution supplementing a dietary devoid of fruits and vegetables but simulating a normal adequate ration in proximate composition and vitamin content. It has been concluded that the findings by others of an enhanced biological potency for the ascorbic acid in fruits and vegetables is not due to the presence in such natural products of a factor which permits greater absorption and more effective utilization of the vitamin. [The expenses of these studies were defrayed by a grant from the Duffy-Mott Company, Inc, New York, N Y.]

Effect of sugars, sugar alcohols and gastric mucin on utilization of tocopherol in muscular dystrophy. A T MILHORAT and W E BARTELS (by invitation) *Depts of Psychiatry and Medicine Cornell Univ Medical College, The Russell Sage Inst of Pathology and the New York Hospital, New York, New York* Our previous investigations showed that wheat germ and the gastro intestinal tract of normal subjects contain factors that further the utilization of alpha tocopherol in progressive muscular dystrophy. Inositol and propylene glycol had similar effects suggesting that these factors might be sugar alcohols or perhaps sugars. These effects were a decrease in creatinuria and an in-

crease in creatinine output of patients when tocopherol was given orally with these substances. Alpha tocopherol alone was without effect. The present investigations suggest that the factors are carbohydrates in gastric mucin and in pectin of wheat germ. Galactose and mannose which are present in both of these natural materials had pronounced effects. Arabinose, present in pectin, and 1-fucose present in gastric mucin had moderate effects. Galactose given in the form of lactose had no effect in 1 patient whereas when given as raffinose for 3 days it reduced the creatinuria 35-50 per cent for 2 weeks. Ribose, xylose, rhamnose, adonitol, glucosamine, levulose, glucuronic acid, galacturonic acid, ascorbic acid and phloroglucinol did not affect creatinuria when given with tocopherol. Arabitol, dulcitol and mannitol had slight effects. During the period of mucin feeding, the urinary nitrogen was increased suggesting that the mucin was digested and the constituents were liberated.

The effects of all positive substances varied considerably in different patients and were greatest in the mild forms of the disease [Aided by The Armour Fund for Research in Muscular Disease, and a grant from the Nutrition Foundation, Inc.]

Growth and fertility of the male mouse on synthetic diets. L. MIRONE (by invitation) and L. R. CERECEDO, Dept of Biochemistry, Fordham Univ. In this study the effect of a synthetic diet on growth and fertility in the male mouse has been investigated. The composition of the diet, R 5(a) has been reported (Cerecedo, L. R. and Mirone, L., Arch Biochem 12: 154, 1947). The male colony consisted of 111 animals representing three different strains. At present the youngest member of the colony is 220 days old and the oldest member is 513 days. The animals were placed on the synthetic diet at weaning and when they were 75 to 90 days old they were mated with stock females. Thereafter, they were mated every 3 months. The results obtained are listed below.

Diet	No. of animals	1st	2nd	3rd	4th	5th mating
Stock	Mated	23	19	8	3	2
	Successful matings	22	16	7	1	2
R 5(a)	Mated	29	24	16	4	1
	Successful matings	25	22	12	3	1

Growth of the male mouse on this diet compares favorably with that on the stock diet. The average litter size resulting from matings with stock males is 6.2 and with experimental males 6.9. The addition of supplements of folic acid or first urine eluate liver fraction had no effect on the fertility. These results indicate that diet R 5(a) is complete

in so far as growth and fertility of the male mouse is concerned [Aided by a grant from the John and Mary R. Markle Foundation].

The effect of dietary fat level on the physical capacity of rats during undernutrition. MARGARET G. MOREHOUSE (by invitation), BRADLEY T. SCHEER (by invitation) and HARRY J. DEUEL, JR., Univ. of Southern California School of Medicine. Weanling rats were fed ad libitum diets varying in fat content from 0 to 40% for a period of fifteen weeks. Each group was then equally divided into two new groups where the diet contained 5% or 25% of fat. The latter diets were fed at a level of 20 calories for a 300 gram rat per day which caused a weight loss on the average of approximately fifty per cent over 12 weeks. After twelve weeks the surviving animals were again continued on the same diets ad libitum. Their physical capacity was determined by a swimming test (Scheer, Dorst, Code and Soule, Am J Physiol, in press) at the end of the first ad lib period, after the restricted calorie intake and again after they had regained their original weight.

Animals allowed to attain maturity on fat free diets showed a lower initial physical capacity than those raised on diets containing considerable amounts of fat. Also a greater decrease in physical capacity obtained with rats previously on the fat-free diet when subjected to a 5% fat diet restricted in calories than resulted when given a restricted diet containing 25% fat. However, no differences were noted during the restricted period between the 5 or 25% fat level when the rats had previously been raised on diets containing 10% or more fat. [Work done in cooperation with the Committee on Food Research of the Quartermaster Food and Container Institute of the Armed Forces.]

Riboflavin deficiency in dogs as affected by the basal diet and by desoxycorticosterone. AGNES FAY MORGAN, MARY GOODY (by invitation) and HELEN E. AXELROD (by invitation), Lab of Home Economics, Univ. of California, Berkeley. The study of acute riboflavin deficiency in dogs was continued by feeding eleven young dogs of two litters purified diets which contained respectively, a) 63.3 per cent casein, 30.7 per cent cornstarch, 10 per cent fat, or b) 24 per cent casein, 30.7 per cent cornstarch, 40 per cent fat, or c) 18 per cent casein, 76 per cent cornstarch, 2 per cent fat. One dog on each of these diets was given all necessary vitamins, and two or three were given all the vitamins except riboflavin. The typical collapse seen previously (Fed Proc 5: 236, 1946) occurred in the deficient dogs after 71 days on diet a, 83 to 110 days on diet b, and 94 to 109 on diet c.

One of the deficient animals on diet a and one on diet b were given desoxycorticosterone when collapse symptoms were seen. Immediate alleviation of the hemo concentration, anuria and low

blood chloride and blood sugar levels resulted. The dog on diet a survived 14 days, and that on diet b 23 days under this treatment, when both succumbed, without the sudden collapse syndrome. The characteristic anemia, low liver glycogen and high liver fat were not affected by the desoxyeorticosterone. One of the dogs on diet b and one on diet c were given riboflavin when collapse occurred, with resulting rapid recovery from the dehydration, low blood sugar and chloride levels, gradual increase in hemoglobin and in glucose tolerance, and in 60 to 70 days nearly normal liver composition. [Aided by a grant from the Nutrition Foundation, Inc.]

**Growth of mice on highly purified diets containing mixtures of amino acids.** VINCENT E. NLWE (by invitation) and LEOPOLD R. CERECEDO, *Dept. of Biochemistry, Fordham Univ., New York City*. This investigation was undertaken to determine the possibility of maintaining mice on purified diets containing a mixture of the ten essential amino acids and glycine. The basal diet consisted of salt mixture 4.0%, Ruffex 2.0, Crisco 10.0, corn oil 7.0, cod liver oil 3.0, sucrose 45.07, and sodium bicarbonate 1.72. The best amino acid mixture, having an active amino acid content of 18% and containing seven racemic amino acids, amounted to 27.21% of the diet.

The following supplements were added per kg of diet: thiamine, riboflavin, and pyridoxin 30 mg each, calcium pantothenate 100 mg, inositol nicotinic acid, and p-aminobenzoic acid 200 mg each, alpha-tocopherol 50 mg, folic acid 10 mg, ascorbic acid 1 gram, choline chloride 2 grams.

At least moderate growth (body weight up to 21.8 grams) was obtained with this diet when compared with the growth resulting from the use of control diets. The amino acid mixture was replaced on the control diets by casein, acid hydrolyzed casein, or various enzymatic protein digests at a dietary level of 18%. Growth was excellent on the diets containing casein or the enzymatic protein digests but was somewhat inhibited when acid-hydrolyzed casein supplemented with 1% tryptophan was used.

The slower rate of growth obtained when using diets containing amino acid mixtures or acid-hydrolyzed casein supplemented with tryptophan confirms the belief of other investigators that some unknown factor which is required for maximum growth is destroyed when casein is hydrolyzed with acid.

**Sex differences in biotin deficient rats fed dried whole egg.** RUTH OKEY, RICHARD PENCHARZ (by invitation) and SAMUEL LEPAKOVSKY, *Dept. of Home Economics and the Division of Poultry Research, College of Agriculture, Univ. of California, Berkeley, and the Dept. of Pathology, Mt. Zion Hospital, San Francisco*. Rats were placed at

weaning on diets containing 36 per cent dried whole egg with extracted casein, sucrose, salts, and a crystalline vitamin mixture which included folic acid but no biotin.

Deficiency symptoms appeared after 4 to 6 weeks. The rats became noticeably hypersensitive to touch. Alopecia, in males, was progressive. After several months many of them were almost completely denuded. The texture of the skin appeared finer than usual but there was no dermatitis associated with the loss of hair. Females showed the deficiency more slowly and tended to appear unthrifty and moth eaten rather than to lose hair completely.

Animals continued to gain weight even after alopecia was well established. Administration of biotin produced prompt regrowth of hair and remission of other deficiency symptoms.

Spayed females developed the same deficiency symptoms as intact males but in a shorter time. Castrate males, on the other hand, became denuded somewhat more slowly than intact males. In castrated males with ovarian implants, the animals in which the implants survived and seemed active were resistant to denudation. Loss of hair in biotin deficient rats appears, therefore, to be affected by ovarian secretion. [Part of this work was supported by funds from the Quartermaster Food and Container Institute for the Armed Forces Committee on Food Research Contract W-11 000 Q M 70202.]

**Thiamine and riboflavin intakes and excretions during pregnancy.** HELEN OLDHAM, BERNICE BLUM, SHIRT (by invitation), THIELMA PORTER, *Dept. of Home Economics, Univ. of Chicago*. Primiparas, living at home on self selected diets were studied for 9 day periods during each of the last 5 months of pregnancy. All food eaten during the first 7 days was weighed and samples were saved for thiamine and riboflavin analyses. Intakes of other nutrients were calculated. Complete urine collections were made during the 7 days and aliquots of a composite were analyzed. On the seventh, eighth and ninth days, after identical breakfasts, four hour urine specimens were collected. That on the seventh day served as a control and those on the eighth and ninth days as a measure of the returns of riboflavin and thiamine test doses which were given with breakfast.

The average daily intakes of the different subjects ranged from 1000 to 5000  $\mu$ g of thiamine and 1750 to 6900  $\mu$ g of riboflavin, although those of individual subjects remained quite constant from month to month. The high intakes were due principally to voluntary supplementation with synthetic vitamins.

Both average daily urinary thiamine and riboflavin increased progressively with the intake. Those on intakes of approximately 1000  $\mu$ g of thiamine and 1750  $\mu$ g of riboflavin exceeded 200  $\mu$ g

thiamine and 300  $\mu$ g riboflavin. The per cent of thiamine intake excreted was approximately the same for all subjects, usually amounting to from 19 to 25 per cent regardless of whether the intake was 1000  $\mu$ g or 5000  $\mu$ g. The per cent of riboflavin intake excreted increased with the intake, 70 to 80 per cent being excreted on a 6900  $\mu$ g intake. The difference between riboflavin intake and excretion, however, was of approximately the same magnitude for all subjects and in most cases was between 1100 and 1700  $\mu$ g.

Thiamine test dose returns were similar for all subjects while those of riboflavin increased with the intakes. [Aided by a grant from the National Dairy Council on behalf of the American Dairy Association.]

Observations on the nature of the interference of live yeast with availability of thiamine. HELEN T. PARSONS, MARCELLA G. POLISAR (by invitation) and DOLORES M. OTTO (by invitation). *Dept of Home Economics, Univ of Wisconsin, Madison*.

It has been shown that when live yeasts (bakers' type) containing ordinary concentrations of thiamine are ingested by human subjects, urinary thiamine fails to be augmented. Furthermore, the live yeasts tend to decrease the excretion of thiamine from other ingested foods.

To test the nature of this interference, a 5 mg dose of thiamine hydrochloride was fed midway between meals, and doses of live yeast were fed immediately before the meals and before the thiamine dose on the third of a four day uniform diet period.

The increment in urinary thiamine output due to the test dose of thiamine was only about a third of the expected return of *circa* 20% of intake thus indicating that the availability of free thiamine as well as of that combined in food is depressed by live yeast. Thus the interference seems not to be analogous to the interference of brewers' yeast with the availability of pteroylheptaglutamate, postulated by others as the capacity of the yeast to inhibit the action of conjugase.

A more tenable hypothesis for this relative unavailability of food thiamine is the one previously suggested, that is that live yeast may actively absorb thiamine from the contents of the digestive tract, thus withholding it from use by the body.

However, a more complicated hypothesis may be required to explain the apparently undue persistence of low urinary returns of test doses of thiamine during several weeks subsequent to one day of raw yeast dosage for some subjects.

The effect of feeding riboflavin on the fluorometric and microbiological values of milk and urine. P. B. PEARSON, D. W. HOOD (by invitation) and B. S. SCHWERTZ (by invitation). *Nutrition Laby, Agricultural Experiment Station and School of Agriculture, A & M College of Texas, College*

*Station*. Following the administration of two grams of riboflavin to goats the riboflavin values of the milk assayed by the fluorometric method were from 25 to 8 times greater than the microbiological values. Feeding tests indicate that the riboflavin activity of the milk for rats was of the same order as for *L. casei*, and that the fluorometric method gives values that are from 250 per cent to 800 per cent too high.

The discrepancy between the fluorometric and microbiological values for riboflavin was even greater in the urine than in the milk following the ingestion of riboflavin. For the urine the riboflavin values by the fluorometric method were from 8 to 16 times greater than the microbiological values. The riboflavin values by the fluorometric and microbiological methods were in reasonably good agreement for both the milk and urine when a stock diet was fed with no extra riboflavin. The data with goats indicate that when large amounts of riboflavin are ingested that degradation products of riboflavin having fluorometric activity, but not biological activity are formed. These degradation products are excreted by the renal pathway or in the lactating animal may pass through the mammary gland into the milk.

Humans and rats were fed riboflavin at levels of between 20 to 30 times the daily requirements. At these levels of riboflavin intake the microbiological values and the fluorometric values for the urine agreed reasonably well for both species.

The diagnosis of malnutrition. L. B. PETT. *Dept of National Health and Welfare, Ottawa, Canada*. Claims of widespread malnutrition in the United States or Canada are difficult to substantiate in the face of the amounts of food reaching consumers. Since the deaths ascribed to nutritional deficiency diseases are few, such malnutrition must be mild.

There is no agreement on how to diagnose milder cases of malnutrition, nor even on its symptomatology. Dietary surveys compared with present standards can not show malnutrition. (*Canad J Pub Hlth* 36: 69 and 233, 1945.)

Functional tests and biochemical analyses yield useful information, but are restricted in value. Confusion is worst in medical nutrition surveys. Some investigators (*Canad J Pub Hlth* 37: 97 and 399, 1946) use one clinician's impression of nutritional state. Our experience shows that one clinician may make widely varying assessments on different days, and such investigators must show that differences claimed, especially at intervals of time, are not simply a measure of the clinician's variability. Other surveys, such as in Newfoundland or Northern Manitoba (*Canad Med Assoc J* 52: 227, 1945, 54: 220, 1946) list the incidence of individual signs, however vague or unspecific.

These procedures tend to ignore the usual medical procedure of combining all possible information



on each patient, weighing various factors, and then setting up tentative diagnoses for further investigation. Such procedures are occasionally used (New England State Med J 235 151, 1916) and even therapy is demanded for diagnoses (J Am Med Assoc 132 558). Strict criteria combining dietary records over a period of time, biochemical results, and specified clinical results (Canad Med Assoc J 1947, February) are being used in Canada, and regional surveys have shown results such as the following: mild rickets, 11%, nutritional niacin 8%, very few definite diagnoses of riboflavin, niacin, ascorbic acid or vitamin A deficiencies.

**Nutritional status of Burlington, Vermont children.** H B PRINCE, R F KRAUSE (by invitation), J H BROWN (by invitation), SUSAN MERROW (by invitation) with the technical assistance of C A NEWHALL (by invitation), T H HARWOOD (by invitation), P D CLARK (by invitation), R E CORLEY (by invitation), T B TOMASI (by invitation), J C CUNNINGHAM (by invitation), MILLA E NEWLAND (by invitation), RUTH LAW (by invitation), HATTIE KAPLAN (by invitation), ANNE BAKER (by invitation), ELIZABETH PAUSEN (by invitation). *Depts of Biochemistry, Medicine and Anatomy, College of Medicine, Univ of Vermont, and the Vermont State Dept of Health, Burlington, Vermont.* Clinical deficiency lesions, blood vitamin levels and food intakes are being studied on 350 Burlington, Vermont children. These were selected from 900 school children—grades 3 to 8—and had moderate to marked lesions assigned to a deficiency of one or more vitamins. Niacin, riboflavin, ascorbic acid and vitamin A therapy are being given in the treatment of the lesions generally attributed to their respective deficiencies.

Photographs of lesions have been taken in color and in black and white. Seasonal dietary patterns and adequacy of food constituent intake are being determined and reveal a low intake of fruits and vegetables. Milk is widely used but not in recommended amounts.

Bloods have been analyzed according to the methods of Bessey and his associates. Hemoglobin and serum protein levels are predominantly within normal ranges. In the spring, 70 per cent of the serum ascorbic acid values were below 0.6 mg % and in the fall 29 per cent. Corresponding percentages below 0.3 mg % were 28 and 11. In the spring, 52 per cent of the serum vitamin A levels were below 30 gamma per cent and in the fall 17 per cent. Sixty-one per cent of the serum carotene values were below 100 gamma per cent in spring and 52 per cent in the fall. [Aided by grants from the Milbank Memorial Fund, Merck and Company, Inc., National Vitamin Foundation, Inc., and Eli Lilly and Company.]

**Role of gastrointestinal tract of the guinea pig**

in elimination of ascorbic acid given intraperitoneally. MARY ELIZABETH REID (introduced by Helen T Parsons). *Division of Physiology, National Inst of Health, Bethesda, Maryland.* Ascorbic acid (5 mg/100 grams) was injected intraperitoneally into adult male guinea pigs maintained on a pelleted diet devoid of vitamin C. After periods varying from 1 to 24 hours the animals were killed and the contents of the gastrointestinal tracts washed out with 10 per cent metaphosphoric acid. Assays for ascorbic acid were made separately on the contents of the stomach, small intestine, cecum, and colon.

The vitamin was found in the contents of the stomach and small intestine, the amount varying with the length of time after injecting. In the cecum and colon the content ranged from none to very small amounts. These results suggest that the vitamin is excreted into the stomach and small intestine and is destroyed in the cecum. Further evidence that this may be true was obtained in a study made in cooperation with Mr Wm White on the rate of movement of the contents through the different parts of the digestive tract. Fairly rapid passage was observed through the stomach and small intestine and much retardation in the cecum.

**Effect of diet on polyethenoid fatty acids of rat tissues.** IRMA RIECKHOFF (by invitation), RALPH HOLMAN (by invitation) and GEORGE BURR. *Division of Physiological Chemistry, Univ of Minnesota.* A modified alkali conjugation, followed by spectrophotometric measurement of the developed characteristic absorption bands, was used for measurement of the highly unsaturated fatty acids extracted from rat tissues. Lacking absolute values for the more highly unsaturated acids, all tissues were compared with a cod liver oil standard.

Eighty-two female rats were reared on a fat deficient diet. When ten months of age they had reached a growth plateau and had scaly skin. They were then divided into three groups: (1) continued on the fat-free diet, (2) received a daily supplement of 100 mg of corn oil, and (3) a daily supplement of 100 mg of cod liver oil. After 8 weeks some were decapitated and the total fatty acid recovered from blood, liver, kidney, heart, brain, muscle, skin and adipose tissue.

Others from each group were used for separation of phospholipids from neutral fat before saponification and isolation of the free fatty acids.

The conclusions are:

(1) Fat deficient rats contain considerable amounts of hexaene, pentaene and tetraene acids. Some triene is indicated and diene is in doubt.

(2) Feeding of linoleic acid brings about the deposit of arachidonic in heart, liver, kidney, brain and skin but not in muscle or adipose tissue.

(3) Polyene acids are largely in phospholipids.

(4) Polyene acids in fed cod liver oil deposit

largely in a few organs, being most concentrated in the heart

(5) Corn oil is superior to cod liver oil as a curative oil

Tyrosine oxidation by livers from rats with sulfa-induced pteroylglutamic acid deficiency. GERTRUDE RODNEY, MARIAN E. SWENDEID and ANN L. SWANSON (introduced by R. A. Brown) *Research Labs., Parke, Davis & Co.* We have reported preliminary experiments in the Warburg apparatus on the oxidation of tyrosine by liver suspensions from rats with a sulfa induced pteroylglutamic acid (PGA) deficiency. The rate of oxidation of tyrosine by the livers from the PGA deficient animals was shown to be less than that of livers from normal rats, and when 10  $\gamma$  crystalline PGA were added to the livers from PGA deficient rats, the rate of tyrosine oxidation approached that of the normal livers. These studies have been extended and will be considered in detail. In addition, data on the effect of liver extracts and of PGA hexaglutamyl conjugate on the restoration of tyrosine oxidation will be presented.

The PGA deficiency state in rats was produced by placing the animals on a purified diet containing sulfa sulfidine until leucopema developed. Livers from 3-5 animals were pooled and homogenized in a Waring blender. With a concentration of 0.25 mg wet weight per ml the oxidation of 0.5 mg l-tyrosine was determined over a 2 hr period, and compared with oxidation by normal liver suspension at the same concentration. The influence of PGA, PGA conjugate and liver extracts on the oxidation was determined after addition of these to the liver suspensions.

The respiratory quotients (R Q) of normal and diabetic subjects after breakfast and lunch. HOWARD F. ROOT and THORNE M. CARPENTER. *The George F. Baker Clinic, New England Deaconess Hospital, Boston.* The respiratory quotients of the diet of the preceding day and of the breakfasts and midday meals of 6 normal subjects were calculated, and the basal respiratory quotients and those after breakfast and midday meals were determined on 12 days. The same calculations and determinations were made on 24 diabetic patients under dietary and insulin treatment on 30 days. The average basal R Q of the normals was 0.80, the R Q after breakfast was 0.82, and after the midday meal was 0.79. The average basal R Q of the diabetic patients was 0.78, after breakfast, 0.78, and after the midday meal 0.78. The variability of the changes in R Q after the meals, as compared with the basal R Q, was about the same in both groups. With the normals, 64 per cent showed a rise in R Q after breakfast, as compared with 50 per cent with the diabetics. After the midday meal 25 per cent of the normals showed a rise in R Q, as compared with 36 per cent of the

diabetics. The diabetic patients did as well or better than the normals in the combustion of carbohydrates when the differences in the composition of the preceding diets and of the meals are considered. Exceptions occurred in diabetics who had recently had remission and lack of diabetic control with consequent emaciation, or who had gone 1 or 2 days without insulin. Maintenance of normal respiratory quotient relationships in diabetic treatment is desirable.

The chick growth factor of cow manure, a counteractant of effects of excessive soybean meal. MAX RUBIN and H. R. BRIDGEMAN (introduced by N. R. Ellis). *Agricultural Research Center, Beltsville, Maryland.* Chicks fed a diet containing 70 per cent of expeller soybean oil grew at a slower rate and had higher mortality than did chicks fed a diet containing 35 per cent of the same meal. The other constituents of both diets were grains, alfalfa meal, and mineral and vitamin supplements. The unfavorable effect of the high level of soybean oil meal was counteracted by a concentrate of the chick growth factor of cow manure but not by methionine.

This growth inhibiting effect of soybean oil meal is believed to be distinct from the heat-labile trypsin inhibitor of soybeans because it occurs in commercially heated meals, because the growth factor which counteracts it is less effective when fed with raw than when fed with heated meals, and because the growth factor is effective when transmitted by the hen through the egg to the chick, and would thus be expected to function in metabolism rather than in digestion.

The effectiveness of the growth factor is not limited to diets containing soybean products. This means either that it has other functions unrelated to the growth inhibiting effect of soybean oil meal or that the inhibiting effect is exerted not only by soybean products, but also by other materials.

Growth and reproduction of swine on a purified diet. WALTER C. RUSSELL, KLAUS ULLA and ARTHUR E. TEERI (by invitation). *Dept. of Agricultural Biochemistry, New Jersey Agricultural Experiment Station, Rutgers Univ., New Brunswick, New Jersey, Dept. of Pharmacology, Univ. of Illinois Medical School, Chicago, Illinois and Dept. of Agricultural Chemistry, Univ. of New Hampshire, Durham, New Hampshire.* Weanling pigs of 2 litters were maintained for periods extending to 469 days, (a) on a purified diet supplemented with thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, p-aminobenzoic acid, choline, inositol, alpha-tocopherol, and vitamins A and D, (b) on the purified diet (supplemented as in (a)) with an additional daily supplement of 10 grams of dried liver, and (c) on an adequate commercial hog feed (control).

During the first 3 months after weaning, growth

on the purified diet was at least equal to that on the commercial feed, but later hours on the last-named ration gained more than their litter mates on the purified diet. The appearance and behavior of the animals on the purified diet did not depart appreciably from that of the controls. On the purified diet, the animals failed to reproduce, although satisfactory reproduction occurred on the commercial feed.

The addition of dried liver to the purified diet had no consistent effect on growth and did not permit reproduction.

**Vitamin A and basal metabolism.** DULAL PABAI SARDHU (by invitation) and SAMUEL BRODY *Dairy Dept., Univ. of Missouri, Columbia*. Data are presented to show the time course and the level of decline in basal metabolism and in thyroid size following the ingestion of excessive amounts of vitamin A. When 30,000 I U vitamin A per day were ingested by 200 grams rats, the basal metabolism declined 20% in hyperthyroid rats and 10% in normal rats, the thyroid size decreased 35% in normal rats and 20% in thiouracil-fed rats. These effects are explained by assuming that the double bond in the excess vitamin A takes up the iodine from the thyroxine which is thus inactivated while the iodinated vitamin A acts like thyroxine as a depressant of thyrotrophic hormone secretion and therefore as a depressant of the size of the thyroid.

**The inter-relation of vitamin A and cholesterol in the liver of the albino rat.** MIRA M. SIMPSON and LOUISE M. PORTER (by invitation) *Smith College*. Eighty-eight male albino rats of the Sprague Dawley strain with low initial reserves of vitamin A were transferred at weaning or after preliminary periods on adequate diets, at ages of twenty-one to sixty-eight days, to experimental diets for periods of nineteen to twenty-eight days. The six experimental diets were adequate, deficient and excess vitamin A, with and without supplements of cholesterol. In the first series two rats were placed on each of the diets at different ages, and in the second series six were fed on each diet from the thirty-fifth to the sixty-third day.

Gain in weight bore no consistent relation to materials ingested. The total and percentage liver weights were greater in rats fed the excess cholesterol, but were not correlated with the vitamin A content of the diet. The liver content of vitamin A was proportional to its daily intake during the experimental period, but not to the total amount ingested. On the vitamin A deficient diet, the liver content was negligible at the end of nineteen days in the youngest rats with low initial reserves of the vitamin, but appreciable and remarkably consistent amounts were retained in the liver at the end of twenty-eight days in the older animals with adequate initial stores of the vitamin. Rats fed an excess of cholesterol and with high liver

content of this have a slightly lower vitamin A retention than their controls. The liver content of cholesterol, in rats receiving excess which could be calculated, was directly proportional to the total amount consumed, and the older the animal when placed on the diet the greater was the amount retained in the liver. Liver cholesterol was greatest in rats fed vitamin A deficient diets, and, except in the older rats, was least in those fed an excess of vitamin A.

**Amino acid excretion by mice fed deficient diets.** H. E. SAUBERLICH (by invitation), E. L. PEARCE (by invitation), and C. A. BAUMANN *Dept. of Biochemistry, Univ. of Wisconsin, Madison, Wisconsin*. As determined by microbiological procedures, each of sixteen amino acids was found to be present in the urine of mice fed various normal diets. The amounts excreted ranged from 1.4% to 6.1% (mean 2.6%) of the amounts of each amino acid ingested as protein. However, mice fed diets deficient in the essential amino acids, methionine or tryptophane, excreted the other amino acids in amounts ranging from 12.5% to 86.5% (mean 37.3%) of those ingested as protein. Such mice were losing weight rapidly.

To determine whether the high excretion of amino acids was due primarily to the deficiency in the essential amino acids or whether it was a general phenomenon associated with weight loss, other diets deficient in thiamine, pyridoxine, or calories were fed to mice, and the urine analyzed as before. The amounts of the amino acids excreted by such mice were found to be more nearly normal, even though the animals were losing weight. Thus on the diet deficient in thiamine, the percentages excreted ranged from 2.7% of the phenylalanine ingested to 13.6% of the arginine ingested. The mean for all acids was 4.9%.

**Unidentified factors essential for growth and hemoglobin production in foxes.** A. E. SCHAEFER (by invitation), C. K. WHITEHAIR (by invitation), and C. A. ELVEILEM *Dept. of Biochemistry, Univ. of Wisconsin, Madison*. Foxes, both pups and adults, were given a purified ration composed of sucrose 66%, casein 19%, cottonseed oil 8%, cod liver oil 3% and salts IV 4%, supplemented with thiamine, riboflavin, niacin, pyridoxine, pantothenic acid, choline, p-aminobenzoic acid, inositol, folic acid, biotin,  $\alpha$ -tocopherol, and 2-methyl-1,4-naphthoquinone. After about 15 weeks for pups and 36 weeks for adults a deficiency developed characterized by anorexia, loss in body weight, poor quality depigmented under fur, paralysis and death. An anemia similar to that reported by Cooperman et al. (*J. Nutr.* 32:37, 1946) in monkeys was observed in animals developing a chronic deficiency. In acute deficiency the animals died without exhibiting significant blood changes. Autopsy revealed severe fatty, light-colored livers,

fatty degeneration of the kidneys and in some instances an ulcerative hemorrhagic gastritis

Supplementation of the ration with 3% whole liver powder, 2% Wilson's 120 liver extract powder, 3% Lederle's alcohol insoluble liver powder or ascorbic acid did not alleviate the deficiency. Likewise no effect was observed when the casein was increased to 30% or when the level of vitamins was doubled.

The addition of 10% fresh liver or 50 cc of raw milk per day alleviated the deficiency. Six per cent dried brewers yeast restored part of the loss in body weight, however, no hematopoietic response was obtained. Fractionation of the activity in fresh liver will be reported.

The biological dimensions of an infection model suitable for nutritional experiment. HOWARD A. SCHNEIDER (introduced by D. W. WOOLLEY), Rockefeller Inst for Medical Research, New York 21, N. Y. Studies, begun in 1940, on the relation of nutrition to resistance to infection have progressed to a stage permitting the definition of the biological characteristics of the host and pathogen populations which allow the demonstration of dietary effect on infectious disease. In an infection model only the host which is genetically heterogeneous has been found to be plastic to dietary influence, and in such hosts, dietary effects on disease are revealed only when the pathogen population employed is heterogeneous in its composition, i.e., containing cells of diverse capacity to produce the disease. Nine models of a single disease, *Salmonella enteritidis* infection in mice, will be described and data presented to show why in eight of these models, diet is without effect and is uniquely effective in the ninth. Dietary factors for increasing resistance have been found as well as for increasing susceptibility. The epidemiological significance of these findings will be discussed.

Tyrosine oxidation by normal and scorbutic liver extracts. ROBERT R. SEALOCK, RUTH L. GOODLAND (by invitation) and PHILIP L. WHITE (by invitation), Dept of Chemistry, Iowa State College, Ames. With our previous demonstration that normal guinea pig liver slices oxidize tyrosine whereas slices from scorbutic animals do not, further study has been made using cell-free preparations. Homogenates and breis have been made by grinding in the all glass homogenizer or with sand, using phosphate buffer as the extracting agent. The centrifugate has been used in the usual Warburg manometric procedure. Oxidation of L-tyrosine is readily achieved by the extracts from normal liver, the amount of the oxidation being dependent, as in any enzyme reaction, upon the ratio of tissue to substrate. With an amount equivalent to 2 grams of liver per mg of tyrosine, four atoms of extra oxygen per mole of amino acid are consumed in 3 hours in agreement with reports

from other laboratories. With 0.1 to 0.2 gram per mg no appreciable oxidation of the substrate is observed.

Extracts made from scorbutic guinea pig liver have exhibited some ability to oxidize tyrosine. At the ratio of 2 grams of liver per mg of tyrosine, normal and scorbutic tissue are indistinguishable, but at intermediate ratios scorbutic tissue proved, in two series of experiments, 89% and 90% as efficient as normal tissue in the oxidation of tyrosine. At still lower concentrations of tissue, even greater discrepancies between scorbutic and normal liver are observed. Further confirmation of these results will be described and their significance will be discussed.

Inefficacy of orotic and yeast adenylic acids as galactogogues in the rat. ALBERT J. SICA (by invitation) and LEOPOLD R. CERECEDO, Dept of Biochemistry, Fordham Univ., New York 58, N. Y. Read by Title. Orotic acid is known to occur in milk, but nothing is known of its physiological role. The beneficial effect of milk on lactation, which has been found in this laboratory, has led us to supplement our basal diet (diet R 5a) with orotic acid at the levels of 25 mg and 50 mg per kilogram during the period of reproduction and lactation. The basal diet consisted of purified casein 30, Crisco 10, lard 5, Ruffex 2, salts 5 and sucrose 48. The following vitamin supplements were added per kilo of diet: thiamine 20 mg, riboflavin 20 mg, pyridoxine 20 mg, calcium pantothenate 40 mg, choline chloride 500 mg,  $\alpha$ -tocopherol 20 mg, Drisdol 20 drops and Vitamin A 67,500 I.U. in a series of 18 pregnancies studied on Wistar and Sprague-Dawley rats, neither reproduction nor lactation were benefited.

Yeast adenylic acid has been reported to have a beneficial effect in certain nutritional deficiencies. It occurred to us to study the effect of this nucleotide on lactation in rats under conditions similar to those used in the foregoing experiment. While this work was in progress, Nelson et al. (Proc Soc Exp Biol Med 61:74 (1946)) reported observations on lactation leucopenia in rats kept on purified diets. Cerecedo and Vinson (Arch Biochem 5:469 (1944)) had found folic acid to improve lactation performance. Adenylic acid was also supplied at the level of 50 mg per kilo of diet during the period of reproduction and lactation. No evidence of a beneficial effect was found in five rats. [Aided by a grant from The Nutrition Foundation, Inc.]

The beneficial effect of milk on lactation in rats maintained on purified diets. ALBERT J. SICA (by invitation), LEOPOLD R. CERECEDO and LEONARD J. VINSON (by invitation), Dept of Biochemistry, Fordham Univ., New York 58, N. Y. Read by Title. The basal diet (diet R 5a) used in this study consisted of purified casein 30, Crisco 10, lard 5, Ruffex 2, salts 5 and sucrose 48. The following vitamin

supplements were added per kilo of diet: thiamine 20 mg, riboflavin 20 mg, pyridoxine 20 mg, calcium pantothenate 40 mg, choline chloride 500 mg,  $\alpha$  tocopherol 20 mg, Drisdol 20 drops and Vitamin A 67,500 I U. In agreement with previous results (Vinson and Cerecedo, *Arch Biochem* 3: 389 (1944)), excellent growth but only moderate success in reproduction and lactation was obtained with this diet.

Wistar and Sprague-Dawley rats received from weaning the basal diet alone, or the basal diet supplemented with 2 ml or 4 ml of fresh milk daily. The results are presented below.

Diet	Litters surviving on the third day of lactation	Litters weaned	Young given to nurse	Young weaned
R 5a	18	13	93	71
R 5a + 2 ml milk	24	21	136	120
R 5a + 4 ml milk	20	18	92	82
Stock	42	36	255	226

A beneficial effect was also observed on the weights of the mothers and of the young. It is of interest to note that we now have animals of the fourth filial generation on the diet containing 4 ml of milk and that a rat of the third filial generation has weaned three litters successfully. On the diet containing 2 ml of milk we have animals of the third filial generation. Three rats of the first filial generation on the unsupplemented diet have failed to wean young. Our findings suggest a beneficial effect of milk on lactation in the rat. [Aided by a grant from The Nutrition Foundation, Inc.]

**The role of tryptophane in the nutrition of dogs on nicotinic acid deficient diets.** S. A. SINGAL (by invitation), V. P. SYDENSTRICKER and JULIA MITCHELLJOHN (by invitation). *Depts of Biochemistry and Medicine, Univ of Georgia School of Medicine, Augusta*. Uninterrupted growth and absence of deficiency symptoms during a 91 day period have been observed in dogs on a nicotinic acid deficient diet supplemented with 0.5 per cent *l* or *dl* tryptophane. Growth ceased and other early symptoms of blacktongue appeared within two to three weeks in animals on the deficient diet alone. The administration of either nicotinic acid or tryptophane resulted in a remission of symptoms, growth being resumed within twenty-four to forty-eight hours in most cases, although an occasional animal resistant to cure with either of these substances has been encountered.

Increasing the casein content of the diet from 19 to 40 per cent was without effect in preventing the onset of the deficiency state, whereas a level of 61 per cent was efficacious in one dog observed for a period of 60 days. The addition of either 21 per cent gelatin or zein to the deficient diet was with-

out preventive action. The curative action of nicotinic acid and tryptophane were also here demonstrable. The curative activity of *l* and *dl* tryptophane has been assayed in animals standardized with nicotinic acid.

The administration of tryptophane to dogs results in a prompt increase in various urinary nicotinic acid fractions, resembling other species in this respect.

**Further studies in reproduction and lactation in rats fed natural rations.** ROBERT R. SPITZER (by invitation) and PAUL H. PHILLIPS. *Dept of Biochemistry, Univ of Wisconsin, Madison*. It has been shown that an all plant ration composed of 75.34% yellow corn, 17.50% soybean oil meal, 5.0% alfalfa meal and 2.16% added minerals was inadequate for reproduction and lactation in rats. Sterility was common in females fed the basal ration. Resorption and toxemia occurred frequently. Young that were born alive died within one or two days after parturition. Death was apparently due to lactation failure and starvation.

Different alfalfa meals and 1:20 liver powders were somewhat variable as supplements to the basal ration. The possibility that the factor or factors necessary to supplement the basal ration may be easily destroyed during processing and storage of these materials is suggested.

In attempts to identify the missing factor or factors, the basal ration was supplemented with minerals, fatty acids, and all known vitamins. When this "fortified" basal ration was fed, good reproduction resulted. This would indicate that reproduction on the basal ration had been limited by a deficiency of one or more known factors. However, these females failed to lactate normally and only 20.0% of the young were weaned. The addition of 5.0% fresh beef liver, 5.0% lyophilized pork liver, an alcohol insoluble fraction of lyophilized pork liver, or 5.0% casein to this fortified ration resulted in marked lactation improvement. Supplementation with addition soybean oil meal was without effect. A lactogenic hormone preparation was variable as a supplemental source of the factor or factors.

Experiments to determine whether the missing factor or factors is (are) protein in nature are being continued. Since the fortified basal ration contained high levels of the known vitamins, minerals, and fatty acids, and since some protein supplements were ineffective, it is possible that the lactation failure may be due to a deficiency of an unknown factor.

**The nature of protein enrichment of refined wheat flour with cultured yeast.** BARNETT SURE. *Univ of Arkansas, Fayetteville*. The nature of protein enrichment of refined wheat flour with cultured yeast was carried out on 180 albino rats. The wheat flour was fed at a 89% level as the

only source of protein, introducing 9.17% in ration. Lysine was administered separately from the ration in daily doses of 5, 10, 25, and 75 mg, producing increases in body weight percentage, during a six-week experimental period, of 62, 55, 94, 115, and 147, respectively. When 5 per cent of the wheat flour was replaced by an equivalent amount of dried cultured yeast (strain G), introducing 10.58% protein in ration, there was an increased growth of 134%. From the lysine content of the G yeast it was calculated that the yeast containing ration furnished about 33 mg lysine daily, and yet the growth secured on it was near that obtained by a supplementation of the basal ration with 75 mg of this amino acid. From these results it would appear that, in addition to lysine, the cultured yeast supplied another factor or factors in the protein enrichment of the wheat flour, the nature of which is still to be determined.

The minimum protein requirements of adult dogs. C. F. WANG (by invitation) and D. M. HEGSTED, *Dept. of Nutrition, Harvard School of Public Health, and Dept. of Biological Chemistry, Harvard Medical School, Boston*. Minimum requirements of protein for adult dogs have been studied by determining the total amounts of circulating plasma protein and hemoglobin, the ratio of available fluids to plasma volume, and nitrogen balance, during periods of nitrogen depletion and protein feeding.

Six normal dogs were fed a nitrogen free diet adequate in calories, minerals, and vitamins during a period of depletion, and this was supplemented with spray dried whole egg protein (approximately 2 mg nitrogen per basal calorie) during a repletion period of 40 days. The items mentioned above were determined at the end of each 10 day period. During the depletion period of 2 or 3 weeks, the average plasma volume, plasma protein concentration, circulating plasma protein, and the total circulating hemoglobin were decreased about 24, 1, 27, and 20 per cent respectively. There was no loss in body weight. After egg protein was given, the daily urinary nitrogen excretion was markedly reduced, nitrogen balance was approximately maintained, the concentration of plasma protein and body weight were practically constant, and the total amount of circulating plasma protein was somewhat higher than at the end of the depletion period. Methionine addition to the diet caused no increase in plasma protein production. Great variations in hemoglobin content were found to be universally related to changes in plasma volume, while the total circulating hemoglobin remained relatively constant. The ratio of extracellular fluid to plasma volume remained within the normal range.

From the foregoing evidence, it appears that 2 mg of nitrogen per basal calorie given as whole egg

protein approximates the minimum nitrogen requirement for maintenance in the adult dog.

The protein efficiency of soybean flour as related to its trypsin inhibitor content. R. J. WESTFALL (by invitation) and S. M. HAUGE, *Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa., and the Dept. of Agricultural Chemistry, Purdue Univ., West Lafayette, Indiana*. A method is described for estimating the trypsin inhibitor content of soybean products. The inhibitor was extracted at pH 11, and various amounts of the extract were incubated with definite amounts of casein and of pancreatin. The tryptic activity was found to be inversely proportional to the amount of inhibitor present when 60% or more of the tryptic activity remained.

Raw soybean flour was heated at various temperatures in the presence of water. Destruction of the inhibitor was complete at 108°C which produced the flour with the highest protein efficiency (grams gained per gram of protein consumed). Using lower temperatures, the protein efficiency was inversely proportional to the inhibitor content, in the range of positive N balance. This indicates that the inhibitor is the chief cause of low protein quality in raw or poorly heated soybean products. Autoclaving above 108°C decreased the protein efficiency.

The addition of an inhibitor concentrate to diets containing either heated soybean flour or casein decreased the protein efficiency. The effect of the addition to heated soybean flour was roughly the same as would be expected from interpolation of the results obtained with partially heated soybean flours.

The true digestibility of the protein of raw soybean flour was significantly lower than that for autoclaved flour, while the metabolic fecal nitrogen was higher with diets containing raw soybean flour.

Dietary fat and the nitrogen metabolism of rats fed protein-free rations. WANDA WILLMAN (by invitation), MIRIAM BRUSH (by invitation), HELEN CLARK (by invitation) and PEARL SWANSON, *The Nutrition Lab., The Foods and Nutrition Section, Iowa Agricultural Experiment Station, Iowa State College, Ames*. Studies of the metabolism of rats fed diets containing traces of nitrogen suggest that the presence or absence of dietary fat may profoundly affect the course of nitrogenous metabolism.

Five test rations were prepared, fat either being eliminated entirely or incorporated by weight in quantities equivalent to 5, 10, 15, or 20 per cent. After feeding each diet for 11 days, nitrogen balances over 7 days were determined. Then each diet was fed for another 11 days in quantities equivalent to 100, 75, 50, or 25 per cent of the amounts ingested in the first metabolism period, collections being made again in the last seven days.

Some typical data follow. Rats fed the high fat diet supplying adequate calories excreted 114 and 94 mg of urinary nitrogen per 100 grams of body weight in periods I and II, respectively, those fed the low fat diet, 106 and 76 mg. With calories limited to one fourth the normal intake, excretions were high-fat diet, 108 and 242, low-fat diet, 111 and 415.

The picture does not seem to be one of catabolic breakdown to meet energy needs because rats on the low-fat diet consuming one fourth of the calories needed have a metabolism characteristic of rats fed the high-fat ration when 1 mg of methionine nitrogen is added to the ration. Also, the inclusion of 15 per cent of fat in the diet prevented the untoward destruction of body tissue at the lowest level of calorie intake.

**Strepogenin activity of peptides of glutamic acid.** D. W. WOOLLEY, *The Rockefeller Inst for Medical Research*. Since extensive studies of the properties of the growth factor strepogenin occurring in enzyme digests of proteins have led to the conclusion that it is a peptide containing glutamic acid and glycine, a number of peptides derived from these amino acids were prepared and tested for biological activity in the strepogenin assay with *Lactobacillus casei*. Several of the compounds were previously unknown and had to be synthesized either by the usual acid chloride procedure, or by a special modification of the azide

method in which tosylated amino acids were employed.

Several glutamic acid-containing peptides were active. Thus, compared to a liver standard of potency 1.0, seryl glycyL glutamic acid (SGG) had 1.0, alanyl glycyL G 0.3, glycyL seryl G 0.3, glycyL alanyl G 0.3 and glycyL G 0.1. Prolyl G and glycyL alanyl leucyl G were inactive. All these peptides behaved as did naturally occurring strepogenin in that their potency was unaffected by autoclaving them in the basal medium. Several derivatives in which the gamma carboxyl group of glutamic acid was in peptide combination exhibited considerable activity, but this was largely or totally lost on heating. Thus glutamine had a potency of 200, glutathione 10, and glutamyl bis-(SGG) 1.0. These gamma glutamyl peptides differed further from natural strepogenin in that the response curve rose much more steeply, and reached its maximum at only about 50 per cent of the value attained with the standard. All alpha glutamyl peptides tested were inactive either before or after heating. These included isoglutamic, isoglutathione and glutamyl tyrosine imide. Thus, no substance was found which equaled the potency of the best concentrates of strepogenin prepared from natural sources, although SGG approached it.

Several analogous peptides of aspartic acid (e.g. SGA and GSA) possessed anti strepogenin activity rather than growth promoting power.

## THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

### THIRTY-FIRST ANNUAL MEETING

Chicago, Ill., May 18, 19, 20, 21, 22, 1947

(For possible corrections in any of the following abstracts see the next issue)

**Studies on Tularemia III. Immunization of white mice.** L. L. CORRELL (by invitation), C. M. DOWNS, and M. P. CLAIR (by invitation), *Univ of Kansas, Dept of Bacteriology, Lawrence, Kansas*. The authors, in the course of other experiments, observed that although vaccinated mice usually succumbed to a small inoculation of virulent organisms, the pathological changes seen in the tissue sections of the liver and spleen were appreciably more localized than those seen in unvaccinated mice. Accordingly, further attempts were made to immunize mice. A number of different antigens were used as immunizing agents. The degree of immunity in various experiments suggested that there was a direct connection between the number of bacterial cells in the vaccine and its efficacy, but repeated vaccination did not appreciably increase the degree of immunity.

Although the level of immunity following vaccination was never high, it was sufficient to enable approximately 35 per cent of the animals to resist 4 to 5 LD<sub>50</sub>. Death, when it occurred in vaccinated

animals, was delayed, and a large number of the vaccinated mice harbored a latent infection after recovery. The percentage of animals with latent infection gradually decreased, indicating that the mouse was capable of eliminating the infection over a period of weeks after inoculation. When mice, 30 per cent of which presumably had latent infections, were re-inoculated, only 11 per cent survived, indicating that the latent infection did not serve to protect the mice. Convalescent mice were not significantly more immune to re-inoculation than the vaccinated.

Although the vaccinated mice regularly produced agglutinins following infection, the relation of such agglutinins to immunity and to the presence of latent infection was not clear. Vaccinated mice which survived inoculation as long as 10 to 12 days, showed a level of antibody titer which was higher than that during the post-vaccination period.

**Purification and concentration of influenza virus by means of alcohol precipitation.** HERALD R. COX, JAMES VAN DER SCHEER, STEWART AUSTON



and EUGEN BOHNEL *Viral and Rickettsial Research Section, Lederle Labs Division, American Cyanamid Company, Pearl River, New York* The possibility of sensitization to chick embryo proteins in the use of influenza vaccines prepared from chick embryo material make it desirable to obtain influenza virus preparations of a high degree of purity Of the various methods evolved to concentrate influenza virus, the one developed by Stanley, and by Taylor *et al*, in which the Sharples super-centrifuge is used, appears to be the method of choice for obtaining concentrated and purified preparations relatively free from inactive non-viral protein However, the Sharples centrifuge method is not ideal for large scale production of influenza vaccine since a single machine operating under optimal conditions can handle only 15 to 20 liters of infected chorioallantoic fluid per hour Therefore, efforts were made to develop a procedure that would retain the desirable features of the Sharples centrifuge method but in addition be more suitable for large scale production

It was found that precipitation of proteins by alcohol could be used successfully to concentrate and partially purify the PR8, Weiss and Lee strains of influenza virus under controlled conditions of alcohol concentration, temperature and pH Carefully controlled precipitation with methyl alcohol produced no virus deterioration or loss of activity as judged by chicken cell agglutinating activity, infectivity titers in chick embryos, or immunizing potency of killed vaccine in mice This technique is particularly valuable for large scale production of vaccine when combined with the Sharples centrifuge method and effects great savings in man and machine hours

Resistance induced by vaccinia virus to pertussis infection in mice GILBERT DALLDORF (by invitation), SOPHIA M COHEN, and JULIA M COFFEY *Division of Labs and Research, New York State Dept of Health, Albany* Definite resistance to pertussis infection in mice was induced by vaccinia virus Death was delayed or prevented if the mice were injected with vaccinia virus intracerebrally at intervals of from one to nine days prior to the inoculation by the same route of approximately 1000 bacilli of a phase I *Hemophilus pertussis* strain that had an LD<sub>50</sub> of from 100 to 200 bacilli The state of resistance was well developed in seven days It could be induced by all three of the virus strains studied, a commercial smallpox vaccine, a testicular strain, and a neurotropic strain Effective doses of virus injected in 0.04 ml amounts varied from a 1:10 dilution with the vaccine to 1:50,000 with the neurotropic strain Heated virus suspensions were ineffective This phenomenon, in so far as studied, appears to be similar to the "interference phenomenon," "sparing effect," or "required non-

specific cellular resistance" which has been shown to occur with certain viruses

The commercial smallpox vaccine, avirulent for mice in a 1:10 dilution on injection into the brain, also interfered with the development of fatal infection due to the neurotropic strain administered intracerebrally in a dilution of 1:100 In this case, resistance was established in twenty four hours following the injection of smallpox vaccine

Biophysical studies of blood plasma proteins immunological properties of  $\gamma_1$ -globulin from the plasma of normal humans H F DEUTSCH, R A ALBERTY, L J GOSTING and J W WILLIAMS (by invitation) *Univ of Wisconsin, Dept of Chemistry, Madison, Wisconsin* It has been possible to separate from normal human blood plasma a protein other than fibrinogen with an electrophoretic mobility between that of normal serum gamma globulin (gamma two) and the typical beta globulins It has been designated as gamma-one globulin It has interesting physical and biological properties Unlike the gamma two globulin which is substantially homogeneous as regards molecular weight, it contains from 10 to 25% of a protein with molecular weight of approximately six times the normal value

This new protein contains certain of the antibodies which are associated with gamma two globulin In addition it contains most, if not all, of the Typhoid "O" agglutinin and the beta hemagglutinin This hemagglutinin is carried exclusively by the portion of heavy molecular weight, but only a small portion of this heavy component is associated with the hemagglutinin activity

Immunological studies with gamma two globulin, gamma-one globulin, fibrinogen, and albumin, all essentially homogeneous as regards electrophoretic behavior, demonstrate that such products are by no means pure from a biological point of view There are strong cross reactions of these proteins to rabbit antisera to the four substances

In its electrophoretic mobility the gamma one globulin is analogous to the so-called "M" component of the sera found in certain types of multiple myeloma Thus, studies with gamma-one globulin may serve to further our knowledge of changes in the serum proteins in such pathologies

Complement activity of human serum with especial reference to malaria ANNA DEAN DULANEY *Univ of Tennessee, College of Medicine, Memphis* The complement activity of human serum, as measured by the amount in milliliters required to produce 50 per cent hemolysis, was determined for 87 samples of blood These comprised 45 patients who had received therapeutic malaria as treatment for neurosyphilis, 22 hospitalized patients with a variety of clinical findings, and 20 healthy individuals The malarious patients included 23 with demonstrable parasitemia (rang-

ing from positive thick film to 20,461 parasites per c. cm., and 22 patients with no demonstrable parasites)

The amount of complement required for 50 per cent hemolysis ranged from 0.0028-0.0061 (mean of 0.0043) for the malarious patients with parasites, 0.0031-0.0067 (mean of 0.004) for the malarious patients with no parasitemia, 0.0017-0.007 (mean of 0.004) for the hospitalized group and from 0.0033-0.007 (mean of 0.0043) for the healthy individuals. There was no significant difference in the complement activity of patients making up these 4 groups.

There was no relationship between 1) the complement activity of malarious sera and parasitemia, 2) complement activity and stage of disease, or 3) complement activity and the cephalin cholesterol flocculation test.

A marked constancy of complement (as measured by the amount required for 50 per cent hemolysis) is demonstrated in health and disease followed by recovery. This is emphasized by observations on patients extending over periods of 2-3 months.

Evidence for the neutralization of antigen by reagin. HENRY R. EAGLE (by invitation) and MARY HEWITT LOVELESS, *New York Hospital, New York, New York*. In 1926 Levine and Coca, testing sensitized sites with reagin allergen mixtures, concluded that reagin lacks the capacity of conventional antibodies to neutralize its antigen. Coca and Grove had previously shown that the converse is true, viz., the allergen does neutralize its reagin. This situation, in which one of a pair of specific reactants is neutralized whereas the other remains active, places reaginic antibodies in a unique category. The present experiment was planned to test this assumption.

Initially the problem was approached by testing reagin-antigen mixtures in normal skin, then detecting any unbound antigen by means of reaginic serum introduced into the site on the following day. Interpretation of results was confused by technical complications. The next step was to use the naturally sensitive conjunctiva as a medium for detecting the presence of free antigen in these mixtures. Increasing strengths of antigen were added to constant volumes of reaginic serum and to other control tubes containing either normal or heat-inactivated reaginic serum. The mixture producing the threshold response in the eye was then noted for the reaginic and for the control series. It was learned that antigen mixed with reagin produced no response until definitely more antigen had been introduced than was required in control tests of the other eye. This elevation in threshold was attributed to inactivation of antigen by unheated reagin.

It was interesting to note that normal conjunctivae failed to react to reagin-antigen mixtures even in high concentrations of both components.

This stood in contrast to normal skin which responded promptly to such mixtures by wheal formation. The reactions obtained in sensitive eyes from reagin-antigen mixtures must be interpreted, therefore, as being due to excess antigen rather than to reagin-antigen combinations formed *in vitro*.

If these observations can be substantiated by further experiments which are under way, reagin must be assumed to neutralize its antigen in the manner of conventional antibodies.

The quantitative estimation of egg and chicken proteins in equine encephalomyelitis vaccine. LEWIS L. EAGLE and RAYMOND RANDALL (by invitation), *Laby Division, Army Veterinary School, Medical Dept Professional Service Schools, Army Medical Center, Washington, D. C.* The increasing use in humans of vaccines prepared from viruses cultivated in the embryonated hen's egg brings with it the risk of sensitizing certain subjects to egg and chicken proteins and of inducing undesirable reactions in individuals already sensitized to one or more of these substances. These considerations make it desirable both to reduce to a minimum the non-virus components in such vaccines and to develop methods for the quantitative estimation of proteins derived from the egg or chick embryo which may be present in the vaccines.

The estimation of a single protein in a complex mixture of proteins is only possible if a highly specific method is available. The successful application of the quantitative precipitin reaction to the estimation of pneumococcal polysaccharides and serum proteins suggested that such a method might be applicable in the present case. Hence, standardized rabbit antisera to ovalbumin, a crude ovaglobulin fraction, and chicken serum albumin and globulin were prepared and utilized for the estimation of these proteins in equine encephalomyelitis vaccines of various degrees of refinement.

The data obtained demonstrate that the vaccine obtained by a two stage centrifugation process have a lower absolute content of the proteins tested for than either the crude horse type vaccine or a sample of a commercial human type vaccine. Further data indicate that a satisfactory recovery of protein added to samples of the vaccine may be obtained by this method.

Some relations between equine encephalomyelitis virus (Eastern type) and normal host cellular constituents. LEWIS L. EAGLE and RAYMOND RANDALL (by invitation), *Laby Division, Army Veterinary School, Medical Dept Professional Service Schools, Army Medical Center, Washington, D. C.* A fundamental problem in the characterization of animal viruses is the differentiation of the infective entity from host cellular components possessing similar physico-chemical properties, or, alternatively, the determination of whether the

infective entity, in addition to infectivity, carries with it immunological specificities derived from its host

The development of a method for the purification of equine encephalomyelitis vaccines of chick embryo origin by a two stage differential centrifugation process has made available material believed suitable for investigation of this point. Rabbit antisera were prepared to normal chick embryo proteins isolated by a method similar to that used in the concentration of the virus and were standardized against the homologous antigen by the quantitative precipitin reaction. When such antisera were titrated against a preparation of virus it was found that greater amounts of antigen nitrogen were required to precipitate the same amount of antibody nitrogen than in the case of the homologous normal chick antigen. From the relative amounts of antigen nitrogen the proportion of normal component in the virus preparation was calculated to be 56-77%. The infectivity of the virus preparation ( $9.5 \times 10^{10}$  LD<sub>50</sub>/mg N) was of the same order of magnitude as the highest recorded in the literature.

These data suggest an intimate relation between the virus of equine encephalomyelitis (Eastern type) and antigenic groupings characteristic of the host in which the virus is cultivated.

Studies on immunizing substances in pneumococci. XIV. The distribution of specific polysaccharide in mouse tissues after injection of a "paralyzing" dose. LLOYD D. FELTON, and (by invitation) BENJAMIN PRESCOTT, GLADYS KAUFMAN, BARBARA OTTINGER. *Division of Infectious Diseases, National Inst of Health, Bethesda, Maryland*. In our studies on the effect of the antigenic polysaccharide of pneumococci in man, it has been observed that a certain low percentage of individuals especially in upper age brackets, fails to produce serum antibodies in response to an immunizing dose. In mice, as earlier reported, a relatively large dose type specifically "paralyzes" the immunological mechanism. The duration of paralysis, then reported to be at least 3 months, has now been found to continue for 15 months, almost the life span of the animal. To determine whether or not this paralysis might be due to the presence of specific polysaccharide in the animal, attempts were made by several well known methods to isolate this antigen from various tissues of the body and test by the usual precipitin technique against immune serum with normal serum as control. Tissues of normal mice were similarly studied. Briefly, from observations of a large number of "paralyzed" mice, the pneumococcus polysaccharide was found present in the following tissues, in order of decreasing precipitin titer: liver, spleen, kidney, skin, bone marrow, irregularly present in muscle (especially Type III), lung,

intestines, and urine, and absent in heart and blood. In three instances, the polysaccharide was isolated, partially purified, and tested for immunizing activity. Type I, 5 gamma protected against 50,000 lethal doses, Type II, 0.5 gamma against 500,000 lethal doses, and Type III, 5 gamma against 500 lethal doses. Since for Types I and III this titer was lower than that of the polysaccharide originally injected, it is obvious that the isolated antigenic material was impure or its antigenicity was decreased. The amount of polysaccharide in the tissues gradually decreased with increasing interval following injection, but after 15 months, it was still present in the liver of animals paralyzed against Type I and II, and in one experiment Type III. In addition, mice injected with a paralyzing dose of pneumococcus whole cell vaccine, showed a similar distribution of polysaccharide in the tissues.

The interference phenomenon within the psittacosis-LGV group of viruses. ORVILLE J. GOLUB. *Camp Detrick, Frederick, Md.* A study of the interference phenomenon within the psittacosis-LGV group of viruses was undertaken because of the possibility that certain immune reactions observed between members of this group might be based on interference.

Paucity of differentiating features between strains of this group place a limitation on the ability to demonstrate interference. It has been possible, however, to show that an IP inoculation of living meningopneumonitis virus (Cal 10 strain) into mice increased their resistance within two or three days to an IP inoculation of psittacosis virus (6BC strain). Test animals withstood 100X the virus tolerated by controls.

Mice immunized with living psittacosis virus, SF strain, are relatively immune to IC challenge of homologous virus, but not to the 6BC strain. Two days after IC challenge with SF virus, however, SF immunized mice were able to resist 10X the concentration of 6BC virus compared to controls.

Inoculation of living meningopneumonitis virus into embryonated eggs, followed by 6BC virus the next day, reduced the yield of the latter virus to as little as 1% of control yields.

Cal 10 virus, heated 2' or 3' at 56 C, retained its ability to interfere with 6BC inoculated simultaneously. The yield of the latter virus was reduced to approximately 1% of the control yield.

U-V irradiated 6BC interfered with the growth of living Cal 10, reducing the yield to less than 5% of the control virus.

The exudative process shown by microorganisms in serologic reaction. JAMES A. HARRISON and ELIZABETH H. FOWLER (by invitation). *Dept of Biology, Temple Univ, Philadelphia 22*. Studies done with ordinary microscopy, dark-field micro-

scopy and phase microscopy reveal that the reaction of various species of ciliated protozoa in low dilutions of homologous antisera includes the development of variable amounts of surface precipitate. This product is an amorphous, mucoid substance and is markedly sticky. It first appears in reactions with paramecia at the distal ends of the cilia and later collects over the whole surface. The collection is accompanied by a decrease in the volume contained within the pellicle of the organism. These and other facts observed are taken as evidence that the reaction involves a marked exudative process. Similar reactions are observed in studies with species of the tetrahymena and the glaucoma-colpidium group of ciliates. The precipitate formed is, however, of different consistency in reactions with these groups.

Similar studies on a culture of the genus, *Bacillus*, confirm the stickiness of the product of reaction in low dilutions of antisera reported by others. The bacterial reactions, like those of the protozoa, commonly show a disparity in the amount of extraneous substance which develops about individual cells and between individuals in clumps. Globoid enlargements (or adherents) have frequently been seen along the flagella or at the end, and it appears that the flagella themselves are sometimes sticky or are surrounded by a sticky substance. It is not clear, however, that these observations on the bacteria are attributable to processes involving exudation.

**Effects of complement on the specific neutralization of bacteriophage.** A. D. HERSHEY and J. BRONFENBRENNER, *Dept. of Bacteriology and Immunology, Washington Univ. School of Medicine*. In studying the specific neutralization of bacteriophage, one varies independently the reaction-time and concentration of antibody, and observes activation at a fractional rate proportional to the concentration of antibody, suggestive of an irreversible bimolecular reaction. Exceptions to this behavior have been attributed in the past to heterogeneity among bacteriophage particles. Our study of the effects of complement on neutralization suggest that the conspicuous exceptions are due to the participation in the reaction of heat-labile proteins present in the antiserum.

When present during the reaction between bacteriophage T1 and its antibody, 1:10 complement causes the neutralization to stop at the 10 per cent level of survivors. When T1 is sensitized with antibody alone, then exposed to complement alone, further neutralization occurs if the initial neutralization was less than 90 per cent, but reactivation occurs if the initial neutralization was more complete.

With bacteriophage T2 and its antibody, the effects of complement are the same except for

marked quantitative differences. The neutralization-inhibiting and reactivating effects are best seen with T1, while the neutralizing effect is best seen with T2.

None of these effects are produced by complement heated for 30 minutes at 60°C. Bacteriophage neutralized by complement is reactivated by treatment with papain.

**Anti-reticulo-endothelial serum (anti-reticular cytotoxic serum).** I. PREPARATION and serologic studies. HOWARD C. HOPPS and TOM S. GAFFORD, JR. (by invitation), *Dept. of Pathology, The School of Medicine of the Univ. of Oklahoma*. Antigen consisted of a mixture of eight parts spleen and one part bone marrow from rats which had been perfused *in vivo* with Tyrode's solution. A fine cellular suspension of these tissues, in saline, was injected into rabbits, subcutaneously and intravenously. In certain instances, it was adsorbed on alumina gel and injected intramuscularly. One group of rabbits received antigen which had been lyophilized before administration. In each donor animal, the serologic titer of the serum was determined before and after desensitization *in vivo* to tissues other than those of the reticuloendothelial system, also before and after each sample of serum had been subjected to *in vitro* adsorption with washed rat's erythrocytes. Serologic procedures included quantitative complement fixation studies (using 3 times the 50% unit of complement), a modified collodion particle technique, agglutination studies against suspensions of rat spleen and bone marrow, and determination of hemolytic titers. An evaluation of these methods of preparation and the various serologic procedures employed is presented. The most highly specific anti-reticulo-endothelial serum of high titer occurred in those animals which received multiple intramuscular depots of antigen adsorbed on alumina gel together with subcutaneous and intravenous injections. Both *in vivo* and *in vitro* adsorption with non-reticulo-endothelial elements markedly reduced the hemolytic titers of these serums.

**A quantitative study of the complement-hemolysin relation.** JOHN F. KENT with HELEN M. CONWAY and WILLIE MAE BODIE (by invitation), *Dept. of Serology, Army Medical Dept. Research and Graduate School, Washington 12, D. C.* A precise spectrophotometric method employing the end-point of 50 per cent hemolysis has been used to measure the changes in complement activity that occur when a standard suspension of sheep's erythrocytes is sensitized with graded amounts of a hemolytic antiserum. The results were studied to determine the relationship of the quantities of complement and antiserum which together gave 50 per cent hemolysis. It was found that their

relation may be expressed by the equation

$$y = \frac{\lambda}{b\lambda + a}$$

where  $y$  is complement,  $\lambda$ , hemolytic antiserum, and the constants  $b$  and  $a$  represent respectively the slope and intercept of a straight line which was obtained by plotting the ratio  $\lambda/y$  against  $\lambda$ . The equation is shown to be that of a rectangular hyperbola.

The data were also examined with regard to the effect of hemolysin concentration upon the slope of the hemolytic curve. Taking the constant  $1/n$  in von Krogh's alternation formula as the index of slope, it was observed that the value of this constant approaches a minimum in a central range of hemolysin concentration, and increases progressively with the use of greater or lesser amounts of the reagent.

The observations have a practical application in selecting an optimal concentration of hemolysin for the complement-fixation reaction and the formulation of the complement hemolysin relation would permit the objective definition of this optimum.

**Complement fixation in scleroma (Rhinoscleroma)** MILTON GJELHAUG LEVINE and ROBERT E. HOLT (by invitation) *Inst. of Experimental Medicine, College of Medical Evangelists*. An organism has been isolated from the nose and throat of cases of scleroma (Rhinoscleroma), which has the following characteristics. It is a gram-negative rod which forms large mucoid colonies on eosin-methylene blue agar and nutrient agar. Acid is formed in dextrose, maltose, mannite, and occasionally in sucrose, but never in lactose. This organism is not found normally in the nose or throat and does not correspond to any other bacterium described in the bacteriological literature. It is similar to organisms previously described in scleroma by a few scattered workers (J. A. M. A. 91: 637, 1928; J. Infect. Dis. 55: 150, 1934; Comptes Rend. de la Soc. de Biol., 100: 298, 1929). Etiological evidence published elsewhere by us indicates that this organism may rightly be called *Klebsiella rhinoscleromatis*.

Antigen was prepared from this organism which was harvested after ten days growth on 5% dextrose nutrient broth. The organisms were heat-killed at 65°C for 30 minutes, washed twice with saline and stored in 1/5000 merthiolate in physiological saline solution. Positive complement fixation reactions were obtained with the sera of individual diagnosed as having scleroma. Out of 277 sera from patients suffering from variety of diseases which were submitted for the Wassermann test, 7% were positive. However the complement

fixing titres of these were markedly lower than those obtained from scleroma patients.

**Immunological studies of serum disease I. Fluctuations in the precipitin nitrogen during four months following an acute serum reaction.** MARY HEWITT LOVELESS *New York Hospital, New York, N. Y.* A pollen allergic individual who had had serum disease in childhood sustained a minor injury and received antitetanal horse globulin intramuscularly as a prophylactic measure in the Emergency pavilion. Less than two hours later, she developed marked urticaria locally and generally, and collapsed with acute hypotension. The serum precipitins against the horse globulin were subsequently followed with the Heidelberger and Kendall quantitative method. Whereas only 10 micrograms of antibody nitrogen were detectable on the 5th day after the anaphylactic reaction, there were 190 and 170 micrograms by the 14th and 21st days, respectively. She was then tested intracutaneously with 0.2 ml of 1:10,000 normal horse serum and showed prompt urticarial response. Her conjunctiva responded questionably when one drop of 1:1000 horse serum was instilled and gave definite reaction to undiluted serum. Although the conjunctival sac was flooded with physiological saline and 1:1000 epinephrin, she noted delayed erythema and itching after a few hours for several days. During the same period of time, an urticarial wheal developed daily in areas of skin remote from the test site, the patient felt dizzy and weak, and there were tenderness and weakness of the left wrist joint. On the 28th day, the precipitins had dropped to 118 micrograms of nitrogen. By the 38th day, the precipitin nitrogen was found at 130 micrograms and by the 45th day at 120. Specimens of blood serum taken on the 80th and 121st days, preserved in the frozen state, will be analyzed shortly.

Reagents for normal horse serum and for the immune globulin involved in the patient's reaction were present in the blood, as indicated by passive sensitization studies. After all precipitins had been specifically absorbed out from the specimen taken on the fifteenth day, reagents were still present as evidenced by the sensitizing power of the supernate.

The data suggest the co-existence of reagents and of precipitins for equine immune globulin. Apparently, the production of precipitins reached its peak two weeks after the patient had recovered from her acute serum reaction.

**Determinants of virulence and avirulence in *Salmonella typhimurium*** G. M. MACKENZIE and K. C. BREWSTER (by invitation) *The Mary Imogene Bassett Hospital, Cooperstown, N. Y.* Two smooth strains of *Salmonella typhimurium*, BA and TMO, indistinguishable in cultural, serological,

immunizing, toxigenic, and biochemical characters have for 11 years maintained constant, but widely different, degrees of virulence for mice BA<sub>2</sub> is highly virulent, TMO is relatively avirulent

When BA<sub>2</sub> is grown for 7 days, with daily transfers, in beef infusion broth containing 25% of heat-killed 18-hour broth culture of TMO, a significant decrease in virulence usually occurs. The mean survival time of batches of 25 mice inoculated intraperitoneally with 1000 organisms and observed 28 days increased from 5.6-7.2 days to 15.2-26 days and the percentage mortality fell from 100% to 12-80%. Conversely when TMO is grown for 7 days, with daily transfers, in broth containing 25% of heat-killed 18-hour broth culture of BA<sub>2</sub>, a significant enhancement of virulence occurs, the mean survival time decreased from 23-28 days to 7.2-9.7 days and the percentage mortality increased from 0-24% to 100%.

From these observations it appears that BA<sub>2</sub> contains a heat stable non-antigenic determinant of virulence, and that TMO contains a similar determinant of avirulence.

The minimal infectious inoculum of *S. pallida* in rabbits, and its rate of multiplication in vivo. HAROLD J. MAGNUSON (by invitation), HARRI EAGLE, and RALPH FLEISCHMAN (by invitation). *Laby of Experimental Therapeutics of the U. S. Public Health Service and The Johns Hopkins School of Hygiene, and the Reynolds Research Laby of the Univ. of N. Carolina, Chapel Hill, N. Carolina*. The minimal infectious dose of *Spirocheta pallida* on intratesticular inoculation in rabbits has been found to be one organism. On intracutaneous inoculation, approximately 5 organisms sufficed to infect half the animals.

The incubation period varied with the size of the inoculum, with an average increment of 4 days for each 10 fold decrease in the number of organisms injected. This suggests that the average division time of *S. pallida* in vivo may be on the order of 30 hours. This result agrees with the division time as estimated from the maximum interval which may be allowed between successive injections of penicillin without affecting its therapeutic efficacy.

The determination of the course of infection after inoculation with a calibrated number of organisms offers a quantitative approach to the time at which immunity develops in syphilitic animals, and to its magnitude.

Studies on the immunization of swine against infection with the swine influenza virus. I. Resistance following subcutaneous administration of formalized purified influenza virus. I. W. McLEAN, JR., DOROTHY BEARD (by invitation) and JOSEPH W. BEARD. *Dept. of Surgery, Duke Univ. School of Medicine, Durham, N. C.* A disease easily characterizable and measurable in severity by

height and duration of fever, loss of weight and anorexia was produced in normal, unvaccinated swine by exposure to active swine influenza virus contained in chick embryo chorio allantoic fluid. The animals were uniformly highly susceptible to infection, giving a morbidity score of 94.1 per cent, but no deaths occurred. There was no evidence of synergistic bacterial infection. Vaccination with formalin-inactivated, purified swine influenza virus given subcutaneously produced an overall reduction in the incidence and severity of the clinical disease, resulting in a morbidity score of 59 per cent. No significant difference could be seen between the effects of 1, 2 or 3 injections of 0.5 mg. amounts of the inactive virus, though the respective morbidity scores were numerically slightly smaller with repeated vaccinations. The antibody titers of the vaccinated animals were consistently greatly increased following exposure to active virus, whether symptoms developed or not. The levels of antibody titer 2 weeks after exposure to active virus were related directly to the number of vaccinations preceding the exposure. The reduction in morbidity brought about by vaccination, 37 per cent, was far less than that induced by exposure to active virus, 82 per cent, regardless of the severity or mildness of the disease, and the same was true for animals tested with active virus a second time after previous vaccination and exposure to active virus. The levels of antibody titer of animals in these categories rose little, or not at all, on repeated exposure to active virus, indicating a very low degree, if any, of asymptomatic infection under these conditions. The findings are discussed in relation to their bearing on the control of influenza in man by vaccination.

Latent mouse encephalomyelitis virus as a contaminant. JOSEPH L. MELNICK and JOHN T. RICHMAN (by invitation). *Section of Preventive Medicine, Yale Univ. School of Medicine*. These experiments are concerned with the chance occurrence of latent mouse encephalomyelitis, either the paralytic type (Theiler's original TO strain) or encephalitic type (FA strain of Theiler and Gard) in normal stock Swiss mice. Examples are presented (1) in which TO virus was detected in the brain of a paralyzed mouse, previously inoculated, along with other mice, with human oral washings, and (2) in which FA virus was found as a contaminant of brains and spinal cords of stock mice. This occurred on several occasions during 1944-1946 in mice purchased from two different animal dealers. In one instance, symptoms of a CNS infection with FA virus appeared spontaneously. In the others it occurred following intracerebral inoculation of non-infectious material or of murine adapted strains of human poliomyelitis virus.

In the latter instances, the inoculated murine-

adapted virus and the contaminating FA virus were separated into pure lines of each strain. The contaminated murine adapted human strains were freed of FA virus by treatment with FA hyperimmune serum or by passage through the monkey, a non susceptible host to the FA virus. FA virus was readily obtained from the mixture of strains, by serial passage of brains of mice showing only encephalitic signs or by passage through chick embryos. The virus strains were identified by complement fixation and/or virus neutralization tests as well as by host range and "clinical" signs.

**Distribution of antibody in monkeys paralysed from poliomyelitis virus infection.** ISABEL M. MORGAN, *Poliomyelitis Research Center, Dept of Epidemiology, Johns Hopkins Univ.* Serum neutralizing antibody is notably slow to develop in monkeys convalescent from paralytic poliomyelitis. It has been found, however, that far higher concentration of neutralizing substance is present within certain areas of the central nervous system than in the serum or spinal fluid of monkeys convalescent from Lansing poliomyelitis virus infection. Highest concentration of antibody in such convalescent animals is in the most susceptible anterior horn of the spinal cord, next higher in the medulla, also markedly susceptible, whereas lower concentrations are present in non-susceptible gray areas (amygdala and visual cortex) and low or none in white matter of spinal cord and brain. The neutralizing antibody is specific for Lansing poliomyelitis virus; no neutralization of the immunologically unrelated viruses of Western equine encephalomyelitis and herpes virus was obtained. The antibody becomes demonstrable between 11 and 16 days after onset of paralysis. The bearing of this localization of antibody on immunity to reinfection will be discussed.

A preliminary survey analysis with the euglobulin inhibition method for the serologic diagnosis of syphilis. HANS NEURATH, ELLIOT VOLKIN (by invitation), and H. W. CRAIG (by invitation). *Depts of Biochemistry and Bacteriology, Duke Univ. School of Medicine, Durham, N. C.* Systematic investigation of the serologic differentiation between true and biologic false positive reactions for syphilis (Am J Syph Gon and Ven Dis in press) has led to the following basic procedure: 1) preparation of a serologically active euglobulin fraction by a method of isoelectric precipitation, 2) addition of a heat stable serum inhibitor to a split sample of the euglobulin solution, and 3) quantitative comparison of the serologic titer of the euglobulin solution with that of the euglobulin-inhibitor mixture. In the biologic false positive reaction, complete inhibition of the serologic activity of the euglobulin solution occurs in the presence of standardized amounts of inhibitor, in the syphilitic type of reaction, the euglobulin

solution and euglobulin inhibitor mixture have comparable titers (Mazzini and Cardiophilin antigen emulsions).

The present survey was made on about 2000 human sera of which about 900 were of definitely established diagnostic origin. More than 95% of about 400 biologic false positive sera gave a biologic false positive type of reaction and but 2% a syphilitic type.

Of about 400 positive sera from patients with syphilis, 95% gave a syphilitic type of reaction and but 2% a biologic false positive type. These results were independent of serologic titer, stage of disease and of antisyphilitic therapy. The specificity of the present test in a group of sera of originally undisclosed origin was of the same order as that found in the entire series. [This work was supported by the National Inst of Health, U. S. Public Health Service.]

**Inhibition of glycolysis in mouse brain homogenates by ferrous sulfate.** E. RACKER and I. KRIMSKY (introduced by C. M. MacLeod). *Dept of Bacteriology, New York Univ. College of Medicine, New York.* Homogenates of mouse brain prepared with distilled water have little glycolytic activity. On addition of adenosine triphosphate, diphosphopyridine nucleotide, nicotinic acid amide and  $Mg^{++}$ , glucose is rapidly broken down to lactic acid if addition of  $Na^+$  is avoided. Under these conditions 6 mg (dry weight) of mouse brain homogenate produce 2 mg of lactic acid during the first hour.

If 5 gamma of ferrous sulfate are added to the brain homogenate and the mixture incubated in the presence of glucose for 20 minutes at 38°C, prior to the addition of the coenzymes, the glycolytic activity is depressed by 70-80 per cent. The control brain homogenate, to which no ferrous sulfate was added but otherwise treated in the same manner, loses little or no activity. Diphosphopyridine nucleotide prevents the effect of iron but does not restore glycolytic activity if added after the iron effect has taken place.

In the presence of fructose-1,6 diphosphate, lactic acid production is not inhibited by ferrous sulfate, indicating that the steps leading to the formation of fructose-1,6 diphosphate are inhibited. The glycolytic activity of the brain homogenate inactivated by ferrous sulfate is not restored by crystalline yeast hexokinase and purified preparations of phosphohexokinase. A heat labile fraction from rabbit muscle was found, however, to restore completely the glycolytic activity to the inactivated brain. This fraction has been purified by absorption on alumina gel and by pH and alcohol fractionation and has no hexokinase or phosphohexokinase activity. The relation of these findings to the previously observed inhibition of glycolysis in brain homogenates by neurotropic





## THE AMERICAN PHYSIOLOGICAL SOCIETY

## Abstracts Omitted from Previous Issue

The effect of Intravenous Carbon Dioxide on the Initial Ventricular Deflection of the Electrocardiogram \*THOMAS M DURANT, (by invitation), JOAN LONG, (by invitation), and M J OPPENHEIMER, *Departments of Medicine, Surgery, and Physiology, Temple University School of Medicine, Philadelphia, Pennsylvania* Direct leads from the epicardial surface of the right ventricle of dogs show remarkable changes following the injection of carbon dioxide into the systemic veins or into the right ventricle. These changes appear with a few seconds of the injection and are at their maximum at the time when a mull wheel murmur indicates the presence of a considerable quantity of the carbon dioxide within the right ventricular cavity. There is then a progressive disappearance of the changes which is complete within a few minutes. The changes consist in (1) a marked diminution in the size of the R-wave, and (2) an increase in the depth of the S wave, not proportional, however, to the diminution in size of R. These changes are proportional to the size of the carbon dioxide injection, and in most animal 50 cc results in a complete disappearance of the R wave. Preliminary bilateral thoracic sympathectomy or cervical vagotomy, or both, do not in any way modify the changes. Air injections do not produce a similar effect unless the injection is given within a few minutes of a previous carbon

dioxide injection. The changes with carbon dioxide are not due to the change in pH of the right ventricular blood since injections of dilute hydrochloric acid sufficient to give a corresponding alteration in pH do not have this electrocardiographic effect.

These evanescent, dramatic electrocardiographic changes provide a valuable research tool for the further study of the nature of the excitation process in the right ventricle.

The Interpretation of the Ballistocardiograph Pattern JOHN L NICKERSON, *Department of Physiology, College of Physicians and Surgeons, Columbia University* Further studies on the low frequency, critically damped ballistocardiograph have been made with a view to extending the interpretation of the ballistic record. (I) Distinctive patterns, which will be shown by lantern slides, have been found for such conditions as auricular fibrillation, coarctation of the aorta, ventricular extrasystoles, small stroke volume, arteriovenous fistulas, etc. The circulatory mechanisms involved in these conditions have led to a better understanding of the origin of some of the parts of the ballistic pattern. (II) In those cases where simultaneous ballistic and Fick measurements have been made it is possible by a simple computation to estimate the "force of the heart" as represented by the average velocity of ejection.

\* Aided by RG-194 from the National Institute of Health

## Corrections of Abstracts in Preceding Issue

Page 85 Buschke The word "syncytial" in the last sentence should read "continuous"

Page 100 Edelmann and Stacy The following footnote should be added "This work was done under contract with the Aeromedical Laboratory, Wright Field, Dayton, Ohio"

Page 124 Hartline, Milne and Wagman The following footnote should be added "Work done under Contract N5 ori 122 proj 4, between the University of Pennsylvania and the Office of Naval Research"

Page 130 Hitchcock and Edelmann The following footnote should be added "This work was done under contract with the Aeromedical Laboratory, Wright Field, Dayton, Ohio"

Page 140 Kaulbersz, Patterson, Sandweiss and Saltzstein, in paragraph 3, line 3, the word "was" should read "were"

Page 195 Ryan and Nice Last line, "70%" should be "70%"

Page 231 Wu and Visscher In line 4 of the last paragraph change "2.5 and 5 months" to "2.5 to 5 months"

Page 261 Hier and Bergeim In paragraph 1, line 6, change "es" to "ses", line 7, change "he" to "the"

Page 287 Rubin and Sevringhaus The word "generally" in the last sentence of the second paragraph should read "frequently"

Page 292 Hier and Bergeim In line 11 change

"specimens" to "specimens" and in line 13 change "Illinoic" to "Illinois"

Page 342 Karel and Fleisher Paragraph (6), line 4, "77" should be changed to read "17"

Page 343 Keith and Burchell In line eight the word "fifteen" should read "thirteen" Lines 10, 11 and 12 on the next page should be changed to read "of hyperpotassemia Potassium salts have been used as diuretic agents in chronic nephritis and were given to two of our patients with toxic effects Two other patients received test doses of 5 gm of potassium" In line 18 the words "eleven

of the fifteen" should read "ten of the thirteen" Line 20, the word "eleven" should read "ten"

Page 376 Tabor, Baily and Smith The last three sentences of the last paragraph should read "The decreased hippuric acid excretion correlated well with the diminished para aminohippuric acid excretion The plasma levels of para aminobenzoic acid in the presence of liver dysfunction appear to be higher than in normal subjects This finding is being investigated further as a possible liver function test"

Page 419 Rubin and Bird Insert "meal" after "soybean oil" in second line of text

## NOTES ON THE CHICAGO MEETING, MAY 18, 19, 20, 21, 22, 1947

The thirty-first annual meeting of the Federation was held at Chicago, Illinois, on May 18-22, 1947, at the invitation of the University of Illinois, in collaboration with the other universities, research and teaching institutions in the Chicago area Dr A Burd Hastings, President of the American Society of Biological Chemists, was the Chairman of the meeting

Meetings of the Executive Committee and of the Councils of the Constituent Societies were held on the first day, May 18 The scientific sessions started at 9 A M on Monday, May 19, and continued until 5 P M on Thursday, May 22 On Monday afternoon a joint session of the Federation was held for the first time since the war period and proved to be very popular The size of the audience considerably exceeded the seating capacity (2,500) of the Stevens Hotel Grand Ballroom Only three symposia were presented this year, one by the Physiological Society and two by the Biochemical Society Repeating the procedure of last year, the Physiological Society sponsored a special evening meeting on Monday in the form of a symposium discussion Notable affairs were the Women's Reception and the Static Demonstrations on Tuesday afternoon and evening at the University of Illinois, and the Smoker on Wednesday evening at the Stevens Hotel Several dinners were arranged by Societies and smaller groups with special interests

Although a complete analysis of the registration figures is not yet available, the approximate total registration was 2900, divided about evenly between Society members and non-members, 1,500 copies of the Federation program and 1,200 copies of the Abstracts issue of the Proceedings were sold at the registration desk Total registration showed about a twenty per cent increase over that of last year, but the increase in number of papers on the program was about fifty per cent

It was therefore necessary to arrange for larger meeting rooms and to hold from 12 to 14 sessions simultaneously in the Stevens, Congress and Palmer House Hotels

The continuing growth of the Federation in total membership and size of meetings during and since the war period has produced a difficult situation with regard to meeting places It became acutely apparent that in the future only a few of the larger cities could accommodate the Federation annual meetings Moreover, it was evident that it would be practically impossible to depend on the very pleasant traditional custom of meeting at the invitation of host universities, since no invitation had been forthcoming for 1948 The matter of a future policy for the management and location of the annual meeting became a point of first consideration by the Executive Committee and the Society Councils It was the consensus of opinion that the Federation should no longer impose on the frequently recurring generosity of the exceedingly few university hosts that are located in cities with available accommodations After a very thorough discussion the following significant actions were taken by the Executive Committee and approved by all Constituent Societies

1 Decision to hold 1948 annual meeting in Atlantic City the week of March 15

2 Authorization of funds for additional personnel in the Federation Secretary's office to organize and manage the annual meeting

3 Acceptance of the resignation of Dr Howard B Lewis as Director of the Placement Service, with a vote of appreciation of his invaluable voluntary service to the Federation for the past 15 years Following the recommendation of the Committee on Placement Service the management of this service was delegated to the office of the Federation Secretary

4 Annual assessment per member in all Con-

stituent Societies increased to \$3 00, \$2 00 for Federation Proceedings, \$1 00 for Federation Secretary's office

5 Reappointment of Wilham H. Chambers as Federation Secretary Treasurer

6 Decision to hold a Joint Session of the Federation at the 1948 annual meeting, the program to be arranged by the Society of Pharmacology and Experimental Therapeutics

7 Invitation of the Local Committee to meet in Detroit in 1949 accepted San Francisco or Denver tentatively designated for the 1950 meeting

8 The following recommendations of the Control Committee in regard to counteracting the increased production costs of Federation Proceedings were accepted and made effective

a An increase in price of Part II (abstracts) of

the March issue to \$2 00, making the cost of the total Volume \$4 50 (domestic) and \$5 25 (foreign). This change will become effective with Volume 7, 1948

b Limit the number of reprints to 500 per abstract

c No name shall appear more than once as an author in "Read by Title" abstracts

9 Approved tentative budget for combining the staff of the Federation Secretary's office with that of the Managing Editor of the American Physiological Society publications and Executive Secretary of the American Physiological Society

Dr. Milton O. Lee has accepted the position of Executive Director of the combined offices

## AMERICAN PHYSIOLOGICAL SOCIETY

### SYMPOSIUM ON FUNCTIONAL ORGANIZATION OF THE CEREBRAL CORTEX

PHILIP BARD, *Chairman*

*Johns Hopkins University*

### PATTERNS OF SENSORY REPRESENTATION IN THE CEREBRAL CORTEX

CLINTON N. WOOLSEY

*Department of Physiology, School of Medicine, Johns Hopkins University, Baltimore, Md*

This presentation is primarily a summary of results obtained in this laboratory with the evoked potential technic (1b) in studies of localization patterns in somatic afferent areas of the cerebral cortex of a variety of mammals.

Until recently it was assumed that each of the principal afferent systems has one main pathway into the cortex. Oscillographic studies, however, have shown that touch (1, 30), vision (20, 21), and hearing (33, 23, 24) at least are doubly represented in each hemisphere (Fig. 1 B). We have termed (30, 27) these dual systems somatic areas I and II, visual areas I and II and auditory areas I and II, to avoid imputing to them functional significances and anatomical relationships before these are known. Since in each case it has been customary to refer to area I as the primary receiving area it is a natural tendency to use the word "secondary" in describing these "second" systems. It seems desirable, however, to avoid this usage.

Somatic area I is the postcentral gyrus of primates and its homologue in other mammals. Somatic area II in *Macaca mulatta* lies on the upper bank of the sylvian fissure between the

auditory areas of the lower sylvian bank and the face subdivision of somatic area I in the postcentral gyrus (Fig. 1 C). It is similarly situated between the auditory areas and face area I in other mammals (Fig. 1 A and B). Since in the monkey the face subdivisions of somatic I and II adjoin, the systems are in a sense inverted. Visual area II is essentially a mirror image of visual area I and in the auditory system the pattern of localization in area II is the reverse of that in area I (Fig. 1 B and C). As will be seen the pattern of organization in somatic area II differs in several respects from that existing in somatic area I.

*The evoked potential technic.* When peripheral receptors are stimulated in a normal fashion or when nerve fibers are excited electrically, an "active" electrode placed on the corresponding part of the appropriate afferent area of the cortex, with a second electrode on some inactive tissue, will record a wave like surface positive potential of an average amplitude of about 300 microvolts, with a rising phase of 3 to 6 msec and a falling phase of 10 to 50 msec (1b). The necessary condition for obtaining more or less purely monophasic responses is rather deep pentobarbital

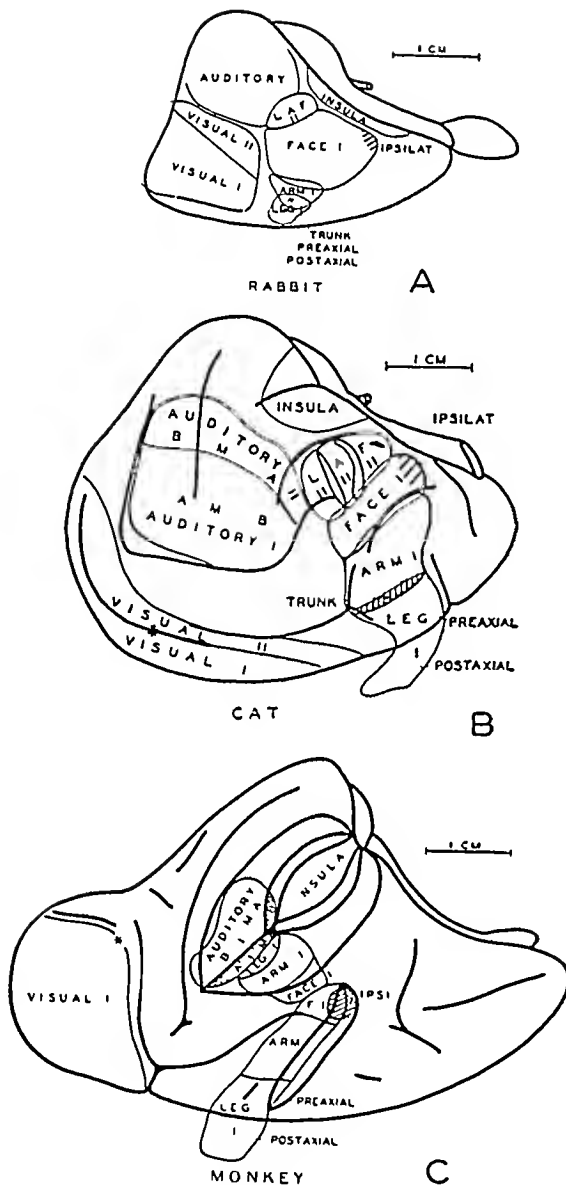


Fig 1 Somatic, auditory and visual areas of rabbit (A), cat (B) and monkey (C) including the ipsilateral face area (hatched lines) as defined by the following studies: rabbit—somatic areas I and II (34), visual areas I and II (21), auditory area (unpublished data of Woolsey and Walzl), cat—somatic areas I and II (1, 15, 25), visual areas I and II (20), auditory areas I and II (33), monkey—somatic areas I and II (5, 31, 25, 26), visual area (Talbot and Marshall), auditory areas (unpublished data of Woolsey and Walzl), ipsilateral face area (30). The letters A, M, B in the auditory areas indicate the regions of projection of the apical, middle and basal turns of the cochlea. In the diagram of the monkey brain the sylvian fissure is represented as spread apart to reveal the insula and the cortex on the upper and lower banks (From Woolsey and Fairman (30)).

anesthesia sufficient to reduce spontaneous activity to a minimum. The evidence indicates that the surface positive wave signals the arrival of impulses at the cortex and that negativity developing after the positive wave, with lighter anesthesia, may be associated with activity leaving the cortex (8, 2). Thus for the mapping of afferent areas a depth of anesthesia sufficient to block synaptic transmission in the cortex is desirable. This state is reached only after the animal has been under continuous pentobarbital anesthesia for several hours. It is the condition under which most of our studies have been made. The results, therefore, define the simplest and most direct relationships existing between the peripheral receptor surfaces and the cerebral cortex. We believe it is important to describe these relations in detail before proceeding to a study of more complicated connections such as those which may be demonstrated by combining the evoked potential and the local strychninization methods.

**Mapping methods.** Two procedures have been employed for defining the relations of peripheral receptor surfaces to the cerebral cortex. With the first, in the case of somatic sensibility, the cortex was explored millimeter by millimeter and for each cortical point examined the cutaneous area capable of activating that point was defined. Data so collected were transformed into figurine charts in which each figurine, mounted in its proper geometrical position on an enlarged drawing of the brain, illustrated the cutaneous area related to that cortical point. Examination of such charts (5, 6, 30, 31) shows the systematic manner in which the cutaneous surface is projected onto the cortex. Each figurine shows that a slightly different part of the body is related to each successive cortical point. The area of skin concerned varies inversely with the degree of cortical representation for the part.

Although the cutaneous area related to a cortical point is different for each point, inspection of the charts will show that a particular spot on the body surface sends impulses to many different cortical points. This fact is most directly demonstrable by the second method of study in which a fixed spot on the skin is stimulated while the recording electrode is moved point by point over the cortex (17, 30). These two methods of study show that a kind of "point-to-point" representation is accompanied by a more diffuse projection and one may imagine that these two aspects of the pattern of representation subserve respectively some aspects of the functions of localization and integration in the cortex.

**The pattern of representation in somatic area I—the postcentral gyrus and its homologues.** When the sensory sequence revealed by the figurine charts of the monkey (5, 6) was compared with the ac-

cepted sensory sequence for man (18) certain new features became evident in the former. In the first place the sequence for the leg was not hip, knee, ankle, toes, perineum, but hip, knee, ankle, toes, ankle, knee, hip, perineum. Between the trunk and toe areas the preaxial aspect of the leg was found, whereas between toes and perineum the postaxial aspect of the leg appeared. In addition, the occipital aspect of the head was found to be represented near the trunk area medial to the center for shoulder and upper arm. These findings led to an analysis of the postcentral area in terms of dorsal roots and dermatomes (31). The analysis showed that the spinal segments from the last caudal through the first thoracic are projected onto the contralateral paracentral lobule and postcentral gyrus in the same serial order as that in which they are arranged in the cord and with overlapping at the cortical level comparable in degree to that seen in the corresponding dermatomes. The serial order of the cervical segments is retained, but on projection to the cortex these segments are reversed *en bloc*. This reversal brings the cortical fields of the upper cervical segments in contiguity with the cortical fields of the upper thoracic segments and places the cortical field of  $C_3$  adjacent to that of the trigeminal nerve. The cervical reversal accounts for the fact that hand and face areas adjoin in the cortex and it also offers an anatomical reason for the face, arm and leg subdivisions revealed by local strychninization (9).

This analysis of the pattern of localization in the postcentral gyrus in terms of dorsal roots has since been confirmed for the leg area by defining the cortical area of responses evoked by direct electrical stimulation of the dorsal roots (29). In addition, however, two new sets of facts have appeared. Besides the postcentral responses which reflect the dermatomal sequence, other postcentral potentials occur which can be accounted for satisfactorily on the assumption that they are derived from proprioceptive afferents in the root stimulated. Moreover, unlike tactile stimulation alone, under deep pentobarbital anesthesia, dorsal root stimulation evokes responses also in the precentral motor cortex. The distributions of the precentral responses for various roots suggest that afferent impulses terminate in a definite way in relation to the pattern of representation in the motor area. These observations suggest methods for studying proprioceptive localization in the cortex.

That the fundamental pattern of representation in somatic area I is basically the same in various mammals is suggested by studies which have been made on the mink (2, 5, 6, 31) and the spider (7) monkeys, on the chimpanzee (32), the cat (1, 2, 15, 30) the rabbit (2, 34) and the pig (30). Even in the rabbit where the hindlimb area is

quite small there is differentiation within somatic area I of centers for pre- and postaxial surfaces of the hindlimb (Fig. 1A).

On the other hand, the degree of development of the various portions of the basic pattern differs from species to species according to the particular somatic differentiations of the individual species. This is well illustrated by the detailed pattern within the hand and foot areas of the monkeys (31, 7) by the highly developed tail area of *Ateles* (7) and by the very large snout area of the pig (3, 30). The face area illustrates well both the fundamental similarity of the basic pattern in different species and the variations in development of the various parts of the face area. These simi-

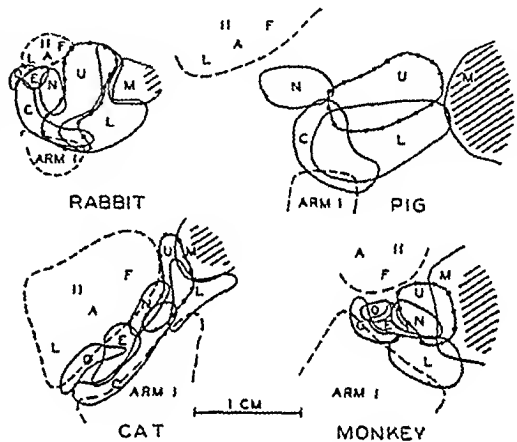


Fig. 2 Diagrams of the face areas of rabbit, cat, pig and monkey to show homologous subdivisions defined approximately by the continuous lines and labeled as follows: O—ear, E—eye, N—nostril, U—upper lip, M—mouth, hatched lines—ipsilateral face (lips, tongue and buccal cavity), L—lower lip, C—side of face. The positions of arm area I and the face (F), arm (A) and leg (L) subdivisions of area II also are indicated.

larities and differences are illustrated in Fig. 2. The diagrams are explained in the legend. Data for the pig are incomplete.

Fig. 2 may also serve to explain why we have chosen to draw the diagrams of the brain upside down, although it is only with the figurine charts that the desirability of so doing is really clear. The reason is that when the face area is viewed in this manner its various parts—ear (O), eye (E), nostril (N), upper lip (U), mouth (M), lower lip (L) and side of face (C)—show the same relationships to one another as do the corresponding parts of the actual face.

**The ipsilateral face area.** In somatic area I the relationship of cortex to skin is strictly contralateral except for a portion of the face subdivision. This we have called the ipsilateral face area. It

Although a lesser topical arrangement has been outlined upon the second sensory areas of each of these three lobes, their anatomical relation to peripheral end organs has not been determined. The remainder of the cortical mantle belonging to the parietal and occipital lobes receive axones from thalamic nuclei which are not directly related to peripheral systems. On the other hand the greater portion of the cortical mantle of the temporal lobe seems to be dependent upon inter-cortical systems.

Unlike the three posterior lobes, the frontal lobe is organized about the origin of a motor system which stems from its precentral gyrus, the corticospinal tract. A second motor area comparable to the second sensory areas of the three posterior lobes is found within the operculum of the frontal lobe, having a reversal of topical localization similar to that found within the second sensory areas (Bailey, personal communication). The region of the frontal lobe known as the area frontalis agranularis (areas 4 and 6) shares a corticopetal projection system from a thalamic nucleus which in turn is not related to a peripheral sensory system, but rather to an enormous bundle of nerve fibers stemming from the nucleus dentatus of the cerebellum. The remainder of the cortical mantle of the frontal lobe, the area frontalis granularis, receives its corticopetal systems from the anterior and medial nuclei of the thalamus.

The control of movement by the cerebral cortex is mediated by the axones of nerve cells which lie within its third, fifth or sixth layers and terminate upon neurones found within sub-cortical groups of nuclei. These axones can be grouped as corticofugal systems which share common terminations (see Hines 1943 for references). Each of the four major divisions of the neopallial mantle in the macaque is the origin of corticofugal systems which terminate within the nuclei of the dorsal thalamus, the nuclei of the brachium pontis and the reticular formation of the medulla oblongata. The superior colliculus in the midbrain receives axones from the frontal lobe (area 4), the parietal (area 7, Peele 1942), and the occipital (areas 18 and 19) and the inferior colliculus from the temporal lobe, while the pretectal nucleus receives fibers from areas 5 and 7 of the parietal lobe. The nucleus ruber receives corticofugal axones from areas 4 and 6 of the frontal lobe, and the subthalamus, from those areas and from 4s, although neither of these nuclei receive any fibers from either the occipital or the parietal lobes. On the other hand the substantia nigra receives corticofugal systems from areas 4, 4s, 6, and 8 of the frontal lobe, from the superior gyrus of the temporal lobes and from areas 3 and 5 of the parietal lobe. The whole of the parietal lobe and

area 1 of the frontal lobe send axones directly into the spinal cord, comprising the parietospinal and the frontospinal tracts (Wagley, 1915). These two tracts pass through the pyramids on their way to the spinal cord. Because of usage and function, only the frontospinal tract which stems from area 1 is classified as pyramidal or corticospinal. The remaining corticofugal systems are classified.

The greater proportion of this striking array of extrapyramidal systems stems from the frontal lobe. Nevertheless, each of these four lobes share certain terminals for their efferent fiber systems and suggest a similar motor organization within each lobe. On the other hand the greater variety of extrapyramidal fibers, originating within the frontal lobe, particularly its greater posterior division suggest a motor organization peculiar to it alone.

In the frontal lobe, the two great cytoarchitectonic regions, namely, the area frontalis granularis, known as the prefrontal cortex, and the area frontalis agranularis, known as the precentral motor cortex, form a convenient line of demarcation for the analysis of the contribution of this lobe to motor activity. Because of certain similarities in the results of electrical stimulation of the former with those obtained from the surface of the junctional regions of the three posterior lobes, the motor activity of the anterior division of the frontal lobe will be considered with them.

Each large division of the monkey's cortex has its adverse field and its own quieting effect. The anterior adverse field in the frontal lobe extends from the anterior border of area 6 over area 8 and encroaches upon Brodmann's area 9. The posterior field spreads over the junctional region of the parietal and occipital lobes with the superior gyrus of the temporal lobe. The adverse movements varied from simple conjugate deviation of the eyes to that of head and eyes. In the anterior field these adverse movements became more complicated, under light anesthesia, to include the axis, the extremities and even the tail. Orientation of the ears were obtained in all except the parietal adverse field. The quieting effect, causing cessation of spontaneous movement, conferring upon the animal a curious appearance of attentive repose, was a generalized effect. This effect was most easily obtained from the anterior field on the lateral surface of Brodmann's area 9 and from the three posterior fields.

Three of these fields yielded other movements of the eyes. Opening of the eyes and dilation of the pupil (Smith, 1944) were elicited from the frontal field, convergence, from the parietal field (Tower and Hines, unpublished) and closure of the eyes and constriction of the pupil from the occipital field (Walker and Weaver, 1940). Outside of these particular areas electrical stimulation



of the area 8 around the caudal end of the fissura principalis (or sulcus rectus) evoked nystagmus as well as conjugate deviation of the eyes and of area 9 (Brodmann) dorsal to that fissure deviation of both eyes either upward or downward. Stimulation of area 17 of the occipital lobe in the macaque (Walker and Weaver, 1940) oriented the eyes toward the visual field represented in the part stimulated.

Besides movements of the eyes electrical stimulation of areas 5 and 7 (Peele, 1944) evoked elevation of the contralateral shoulder (sometimes both shoulders) with or without protrusion of the whole upper extremity. The temporal and occipital fields yielded a complex movement called by Tower and Hines (unpublished) a reaching and grasping act.

Unrelated to any of these results, electrical stimulation of that part of the cingulate gyrus (Smith, 1945) which lies in the frontal lobe produced a complex of responses. These responses included opening of the eyes and dilatation of the pupils, changes in facial expression, vocalization, piloerection, changes in respiration such as arrest, acceleration, increase in inspiratory tone, slowing of the heart beat, increase or decrease in arterial pressure, as well as cessation of muscular movements with relaxation of existing muscular tension.

Of these motor fields only that of area 17 was found within a primary sensory projection area. Each of the other motor fields was unrelated to such an area. Rather they are found in those cortical regions, which receive incoming fibers from the thalamic nuclei of integration. The frontal field receives thalamocortical fibers from the medial nucleus, in which Walker (1938) considers somatosensory and visceral impulses are synthesized, the parietal field, from the nucleus lateralis posterior which seems to combine complex somatosensory functions, and the occipital and temporal fields as well as the most posterior border of the parietal, from the pulvinar in which somesthetic, visual (?), and auditory functions may be correlated.

All of these activities obtained first from the site of origin of the frontoparietal division of the pyramidal tract are clearly extrapyramidal and suggest that orientation of head and of eyes are related to a complex unification of somesthetic sensibility with other types of sensibility at the thalamic level. It is interesting to note that convergence of the eyes was elicited only by stimulation of the parietal field. In the macaque convergence of the eyes relates to stimuli originating from the surface of the body. Constriction of the pupil so far has been found only in the occipital field (Ferrier, 1876, Walker and Weaver, 1940). Of the regions under consideration reaching

and grasping can be related to the synthesis of sight or of hearing with other types of sensibility. Only in the frontal field did adversion reach completion, such that the orienting movement involved the total musculature upon the contralateral half of the body. Does this finding indicate the importance in the economy of the animal body of the synthesis of somesthetic with visceral functions? At the present time the motor activity contributed by the anterior limb of the cingulate gyrus seems to be a special case.

The area frontalis agranularis, the precentral motor cortex, becomes a clear cut extrapyramidal field only after elimination of the pyramidal projection system by surgical intervention (Tower and Hines, unpublished). Under this condition electrical stimulation of any part of this cortical region results in non-topical contraction and non-topical changes in tone of skeletal muscle. Both of these evoked activities manifest a certain organization which in a rough way can be allocated to the architectonic subdivisions of this region, namely, area 6, area 4s, and area 4.

The non-topical contraction of skeletal muscle becomes complex movements characterized by definite sequences which suggest the innervation not only of brain stem mechanisms but possibly of different brain stem mechanisms. The simple flexor and extensor synergies first described by Foerster for man, may in the macaque under light anaesthesia become elaborated into an act. Thus, the flexor synergy, obtained from both lateral and medial surfaces of area 6 encroaching upon 4s posteriorly and area 5 anteriorly may become a complex reaching and grasping act in which the fingers are equally flexed and the thumb adducted. The extensor synergy evoked from the anterior border of area 4 and the adjacent area 6 may become a fully developed diagonally organized activity. Stimulation of posterior area 4 (pyramids surgically divided) may produce less completely developed forms of diagonally organized activity as well as symmetrical extension of all four extremities frequently followed by flexion of one of the four. Although these particular sequential contractions of skeletal muscle may be evoked from any part of posterior area 4, the action is most vigorous and at lowest threshold when the stimulating electrode is localized either above or below the superior precentral fissure, i.e., upon the interregional border between the pyramidal leg and arm fields. Besides these movements, the stimulating electrode elicited from the lateral surface of area 6 a frontal orienting movement which brings the head, eyes, and ears to the midfrontal plane and suggests the state of being on the alert.

So far the electrical exploration of the whole of the cortical mantle of the macaque after surgical

division of the pyramids has not evoked all patterns of movement observed in the living pyramidal preparation (Tower, 1940). On the other hand the extrapyramidal activity elicited by the electrical stimulation of the cerebellar cortex in the cat (Tower, 1936) is almost equivalent to the total activity of the decorticated cat. Consequently, Tower concluded that stimulation of extrapyramidal pathways in that animal elicited patterns of activity determined almost entirely by integration of subcortical centers. This discrepancy between the extrapyramidal organization observed in the living bilateral pyramidal monkey and the results of stimulation of corticofugal systems may have two interpretations. Either the conditions under which these stimulations are performed in the monkey preclude duplication with the observed motor activity in living animal or extrapyramidal activity may be organized in some manner at the cortical level. A migration of the integration of extrapyramidal movement to the frontal lobe in the monkey is suggested by the finding that the electric current is able to elicit all movements observed during life in a macaque from which both frontal lobes, sparing the face areas, had been removed. Although each lobe in the monkey has its own extrapyramidal motor field each of those in the frontal lobe is more developed than any one of those found in the three posterior lobes.

Moreover, the area frontalis agranularis in the macaque has its own extrapyramidal inhibitory action against tone. Inhibition of tonic extension, i.e., standing tone, is obtained from the anterior division of area 4, whereas, inhibition of tonic flexion and release of the grasp is evoked from area 6. The inhibitory action against standing tone is predominantly contralateral and always more effective on the arm than on the leg regardless of the locus of the stimulating electrode. The inhibitory action against tonic flexion is effective bilaterally, contralaterally or ipsilaterally and follows no predetermined sequence. Release of the grasp is often a separate result and its locus is restricted to the anterior border of area 6.

The results of differential ablation of these two areas are in a way reciprocals of those of electrical stimulation. For removal of area 6 was followed by the appearance of the grasp reflex stronger and more enduring in the contralateral hand than in the foot. Removal of the anterior border of area 4, that is, of 4s produced exaggerated standing tone, brisk, irradiating tendon reflexes, hypertonus of the clasp-knife type differentially distributed, clonus, and a minimal residual paralysis (see Hines, 1943, for references).

In resumé the extrapyramidal activity within

the area agranularis frontalis presents a double organization. Electrical stimulation of area 6 produces complex reaching and grasping acts and inhibits tonic innervation of the flexors and releases the grasp, while that of area 4s and its anterior annectant 6 produces diagonal movements used in progression and inhibits standing tone. And when the pyramids are divided, electrical stimulation of area 4 is able to produce complex movements of all four extremities as well as release of their tonic extension. Therefore, both motor and inhibitory action resides in the extrapyramidal systems not only of area 6 but also of the whole of area 4.

This multiple activity of area 4 develops differently in the fetal and infant macaque (Hines and Boynton, 1940). The nonpyramidal type of movement, called holokinesis, can be elicited by electrical stimulation with the 60 c.p.s. sine wave current in fetuses of 66 to 125 days gestation, the pyramidal type, called idiokinesis in those of 135 to 162 days gestation. The receptive points for idiokinesis are clustered posteriorly and separated into three topographical islands by silent areas or loci which yield holokinesis, relaxation of tone (chhalasis) or even tonic innervation of skeletal muscle. After birth, with the passage of time, idiokinesis encroaches upon the more rostral areas in the precentral gyrus. On the interregional borders separating the three topographical areas holokinesis gives way to idiokinesis so that beginning with the fourth postnatal month holokinesis and chhalasis are most easily evoked only from the anterior border of area 4. Nevertheless, in serial stimulation, a locus which yields idiokinesis may later yield both holokinesis and chhalasis when stimulated with a current of different frequency and intensity. The electric current apparently even with the pyramids intact is able to activate corticofugal systems other than the frontospinal tract.

The holokinetic movements so characteristic of the fetal and infant precentral gyrus of the macaque form a complex group—1) Movements of neck and pectoral girdle musculature and of a few muscles attached to that girdle, 2) rhythmical movements of the lips (sucking) and of the tongue (licking), 3) rhythmical movements of the upper extremity, 4) behavior patterns and 5) patterns of progression. Movements of the shoulder girdle and muscles attached to that girdle and of neck musculature were produced by stimulation of the definitive face areas in fetuses (66–125 days) before any sign of pyramidal movement was present. Rhythmical movements of lips and of tongue were evoked from the face area in older fetuses (135–162 days gestation) and in newborns, and rhythmical movements of the upper extremity from the anterior border of the arm area in newborns at a time in development when these areas rarely yielded

idiokinetic movements to exploration by the stimulating electrode. Two behavior patterns were elicited, one from the leg area (infantile defecation pattern) and one from the face area (nursing) during the period in development when they were dominant in the infant monkey's activity. The infantile defecation pattern was never obtained in its entirety. The fractions elicited were,—1) retraction or protraction of the pectoral girdle or of the arm with elevation of the tail, 2) elevation of both shoulders and extension of the tail, and 3) flexion of the contralateral elbow and elevation of the tail. The nursing pattern was evoked as a whole or in part. The total nursing pattern includes not only rhythmical movements of lips and of tongue but also rhythmical flexion and extension of the arms as well as periodic extensor thrusts of both legs. The patterns of progression obtained were the diagonal and the gallop. This variety of movements was not elicited by purposively stimulating the precentral gyrus with supra liminal intensities of the sine wave current, but rather in the course of the attempt to discover the liminal intensity for the area.

Reciprocal innervation of Sherrington so easily produced by electrical stimulation of the mature precentral gyrus of primates seems to be in abeyance during the first postpartum month. For example the three movements which are among those which suffer most severely in the adult macaque subsequent to ablation of area 4, protraction of the arm, retraction of the leg, and supination of the forearm are not evoked by cortical stimulation of area 4 until after the increased resistance offered by their respective antagonists are on the wane. This finding suggests a correlation of maturation of a "chalcastic mechanism" with that of pyramidal initiation.

Fixation was also elicited from these immature cortices by stimulation of loci on area 4 (a few on area 6). Fixation of proximal musculature, accompanied by active contraction of distal musculature can be obtained by stimulation of points so located that contraction of distal musculature is anticipated.

A differential distribution of tone was at times elicited by the stimulation of the interregional borders of the leg, arm, and face areas as well as on the ventral and anterior borders of the precentral gyrus. Chalcasis or the relaxation of tonic innervation was obtained not only by stimulation of the precentral gyrus but also of area 6.

It is apparent that the contribution of the precentral gyrus to the motor activity of the growing monkey cannot be read in terms of the maturation of a single corticofugal unit. Although the corticospinal tract aids in the fixation of proximally lying muscles, initiates discrete and cooperating movements, there are activities in which it takes no

part. Certain types of holokinesis, chalcasis, and tonic innervation are independent of its activity.

At the present time more extrapyramidal corticofugal systems stem from area 4 than we know functions to allocate to them. Further, the frontospinal tract is not in itself a single unit. Whether interrupted in the pyramids or at the cortical level, degenerating myelin is found at the base of the dorsal horn, in the region of Clark's nucleus and among the intermediolateral column of nerve cells in the thoracic levels as well as among the large motor cells of the ventral horn.

Consequently, suprathreshold stimulation of the precentral gyrus of any animal would perforce elicit a multiplicity of muscular responses. That Murphy and Gellhorn (1945) obtained movements of various joints of the limbs or of muscles of the face in co-extensive areas and considerable overlap between the leg and arm or the arm and face subdivisions is to be anticipated. Holokinetic movements obtained in the infancy of the macaque should be able to be elicited later. It is a matter of regret that these investigators did not analyze the movements they produced. Had such an analysis been made we might have gained more knowledge about the contribution to motor activity of some of the many extrapyramidal systems originating in this region, or perhaps of some of the several terminations of the frontospinal system itself.

When the precentral gyrus of a primate is stimulated with threshold intensities of the sine-wave current typical contractions of skeletal musculature are elicited. These results fall naturally into contraction of single muscles or parts of muscles, that of extensor or of flexor groups of muscles as well as innervation of both flexor and extensor groups which in their sequence of contraction resemble the patterns of movement used by the primate in question.

Under nembutal anaesthesia the results of stimulation of the precentral gyrus of the macaque with threshold intensities of the 60 c.p.s. sine wave current in the hands of Woolsey (1938) revealed a detailed pattern of representation of the skeletal muscular system in terms of basic motor arrangements within the spinal cord. In the "leg" area, between the fields for tail and trunk, muscles derived from the dorsal sheet, extensors and abductors, were found represented on the medial surface, those derived from the ventral sheet, flexors and adductors, on the dorsolateral surface. In the arm area the extensors and the flexors for each segment of the upper extremity alternate in strips which cross the precentral gyrus anteroposteriorly. The distal muscles of the arm, in particular the small muscles of the hand are represented in a well defined strip through the area for the trunk and the shoulder as well as in the accepted field for the hand. Behind the central fissure at a corresponding

level of the precentral gyrus Woolsey, Marshall and Bard (1942) found represented the postaxial skin field of the arm which is innervated by  $T_1$  and  $T_2$ . On the motor side the muscles of the hand and wrist are also supplied in part by these two levels. Since the muscles of the hand are also supplied by the lower cervical levels of the spinal cord whereas, muscles of the proximal segments of the forelimb are supplied by higher cervical levels, Woolsey therefore suggests that these findings for the loci of the muscles of the hand could be explained by a reversal of cervical segments in their cortical projection similar to that described for the sensory system in the postcentral gyrus.

Even in the face area Woolsey found that the topical localization of reacting muscles projected on the precentral gyrus is almost the mirror image of the topical localization of the skin area on the postcentral gyrus, as delimited by evoked potentials (Woolsey, Marshall and Bard, 1942). For example the ipsilateral motor face area on the precentral gyrus lies adjacent to the ipsilateral skin area of the face on the postcentral gyrus across the central fissure.

Further, there is overlapping of cortical fields for muscle groups comparable to the overlapping of cortical fields for peripheral skin areas, and individual muscles are maximally represented in specific parts of the precentral gyrus just as areas of skin are maximally represented at particular points on the postcentral gyrus.

That there is in the precentral gyrus of the macaque a detailed pattern of representation of the skeletal muscular system and that the basic plan of this pattern can be analyzed in terms of muscles has been confirmed by a meticulous study of the muscles acting upon or over the ankle joint. Chang, Ruch, and Ward (1947) recorded myographically the simultaneous responses of 8 muscles. The contractions of these 8 individual muscles were isometrically recorded and their threshold and latency of response measured during a systematic exploration of the dorsolateral surface of the precentral gyrus of nine macaques (Goodwin thyratron stimulator set for a frequency of 60 c.p.s., pulse duration 0.5 milliseconds, period of stimulation, 4 seconds, interval between stimulations, at least 3 minutes).

Studied in this manner only one focus for each muscle was found, while the focus of representation of two muscles was never discovered at exactly the same locus although the fringes of these loci for different muscles overlap to a greater or lesser extent. Further, there were intervening silent areas for the 8 muscles attached to the myograph. The anatomical flexors were less responsive than the anatomical extensors, for the flexor point was excitable only to near threshold stimuli. With a stronger stimulus the contraction of the flexor muscle was diminished or completely suppressed.

These investigators concluded that the Betz cells which activate a given muscle are not uniformly spread throughout the region of area 4 which they studied, rather, they are concentrated into fields, the focus of which is peculiar to that muscle. And anatomically these giant cells are concentrated in nests.

The findings of Chang, Ruch, and Ward not only support the analysis of Woolsey but also demonstrate that the topical motor activity of the precentral gyrus can be elicited electrically without its concomitant of topical inhibitory activity. Furthermore, Bosma and Gellhorn's (1946) electromyographical studies of response of antagonistic flexor and extensor muscles to the stimulation of the "motor" cortex show that these muscles (in cat and monkey) under certain conditions can be caused to contract simultaneously without an initial phase of inhibitory activity within the opposing muscle. Consequently, contraction of single muscles and coinnervation of opposing muscles can be obtained by stimulation of this cortical tissue without evidence of the reciprocal innervation of Sherrington and Herring (1897), which Walshe (1946) considers to be "the essence of motor response to cortical activity."

This "essence of motor response" aroused at the cortical level by the electrical current is intimately related to the intactness of the pyramidal tract, for topical contraction of the agonist and its reciprocal of topical inhibition of antagonist disappear together after the pyramids are severed (Fower and Hines, unpublished). And thereafter neither of these activities can be elicited from the precentral gyrus. Reciprocal innervation may be considered less as a specific product of cortical activity as such than as a fundamental characteristic of the segmental mechanism upon which the cortico spinal system is able to act.

Walshe (1946) has urged that 1) because no man can voluntarily contract a single muscle and 2) because no single muscle or groups of muscles are completely paralyzed subsequent to destroying lesions of the precentral gyrus, the basic plan of representation of muscles in that gyrus, as outlined by Woolsey, and by Chang, Ruch, and Ward cannot exist. The inability of man or of monkey to contract a single muscle voluntarily does not abrogate an anatomical relation between the clusters of large nerve cells in area 4 and the motor nuclei of the spinal cord. If no stable anatomical relation between these two regions exists, what a miracle these men have wrought!

It is true in the macaque that small ablations of this cortical tissue rarely paralyze a group of muscles. Rather, they leave the animal dependent upon what remains of the pyramidal and extrapyramidal systems for the innervation of musculature. If only, the extrapyramidal systems remain, all discrete use of skeletal muscles vanishes. But,

if, for example, both of these systems remain in both arm and face areas, these areas are still unable to confer upon the monkey the hand like use of the musculature of the lower extremity so characteristic of his normal activity. Furthermore, the presence of each of these systems in both face areas does not modify the picture of use of skeletal muscle of the extremities from that which characterizes the monkey from which all of area 4 has been removed bilaterally. Apparently, the animal with the former type of operation is unable to utilize the movements of the extremities elicited from the face area by Murphy and Gellhorn with supra threshold stimuli.

There is no one for one correspondence between the results of electrical stimulation of the cortical surface and the utilization of skeletal muscle by the living primate. We have no method of duplicating the multiple impulses which play upon the corticofugal systems in the normal intact animal. And also it is not possible to interpret upon the basis of known anatomical relations of any part of the central nervous system, its functional contribution to the economy of the living animal.

It is not a question of discrete representation versus mass representation of musculature within the precentral gyrus. Both exist. Any analysis of the control of movement made by the precentral gyrus, based alone upon the destroying lesion must consider not only the activity of all the corticofugal systems which stem from that tissue but also all of those which remain in all parts of the cortical mantle. Important as these corticofugal systems are the functional contribution of the corticopetal systems must not be forgotten nor that of the intercortical ones.

In conclusion, each of the four lobes of the monkey's neopallium has its own adversive field and its own quieting effect, located within that part of each lobe which receives corticopetal fibers from thalamic nuclei of integration. Only the occipital lobe in subhuman primates has a motor field within its primary sensory area. When given the opportunity to control motor performance without the aid of the frontal lobe, the three posterior lobes fail to maintain posture or to initiate progression.

Indeed, we might say that the frontal lobe has virtually cornered the control of movement. In particular the anterior division of the precentral motor cortex has assumed the activation of the least stereotyped extrapyramidal action and the control of inhibitory action against tone, which is unassociated with the pyramidal unit. The posterior division of the precentral motor cortex has a basic organization, which is topical both for motor activity and for inhibitory action against tone. These topical activities are dependent upon the intactness of the cortico spinal system. Besides this discrete organization for the control of skeletal muscle, there exists in the same cortical field, a mass organization which survives pyramidal section and is capable of producing not only non topical motor action but also non topical inhibitory action against tone. Both of these systems play their part in the control of movement. Under no known experimental conditions can the electric stimulation of extrapyramidal motor fields yield topical contraction of skeletal musculature. Indeed, it is the discrete organization of skeletal muscle which distinguishes area 4 of the precentral gyrus from all the remaining motor fields of the neopallium of the primate's cerebral cortex.

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## MODES OF FUNCTIONAL ORGANIZATION OF THE CEREBRAL CORTEX\*

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The experiments that gave rise to the following notions were all performed on the primates, *Macaca mulatta* and *Pan satyrus*, although the counts of neurons are usually on man. In all of them the cerebral cortex has come to outweigh and, in neurons, to out-number the rest of the central nervous system. As in all such evolutions of the cephalic end of the dorsal plate, mere size permits greater distinction of functionally dissimilar portions and of their various paths of communication. But with its majority has come not only an undertaking of selected functions of more caudal portions of the dorsal plate and a control of their activity by impulses projected upon them (1), but also interference with the execution of their functions by impulses upon one or more of the systems relaying their signals toward the final common path (2).

Some of those systems, six the cortico-ponto-cerebello-dentato-rubro-spinal (3), have lost so much of their projection upon the cord that the output of their remnants returns in no small measure to the cortex (4), so relating its events indirectly. In primates, the plurality of all lower neurons are thus reentrantly involved. Among remaining caudal systems, I know none which does not receive, directly or indirectly, signals from the cortex, nor any sector of the cortex that does not signal to some of them. But, as they still receive their proper peripheral efferents their output is the result of at least two streams—one from the cortex and one or more from elsewhere in the dorsal plate (5, 6).

To that *great* extent to which its efferents inform it of the peripheral consequences of the action of its own efferents (7, 8, 9), any system is put of the path of a reflex. And most if not all purely reflexive action is negative feedback (10) tending to reduce all deviation from an intended peripheral state measured by the afferents (11). Left to itself each such circuit is homeostatic (9). But, to that extent to which its central nervous components can be influenced from elsewhere, notably the cerebrum, it can be made to seek other states or, to use an engineer's term, be reduced to a *servo mechanism* (11). Nothing but the name is new.

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In 1826 Sir Charles Bell read his famous paper on the nervous circle (7) before the Royal Society, and in 1868 Clerk Maxwell read his on the governors of steam engines (12), with much of the mathematics required for these negative feedback, or reflexive, systems (13). And Hughlings Jackson founded his hypothesis (14, 15) upon their ideas instead of resting it on Herbert Spencer's Epicurean psychology (16) he would certainly not have pictured the second level (17), especially the motor cortex, as the bass of a piano accordion whose every button sounds a chord (17, 18). Nor does he give his theory in admitting cooperation or competition from other structures, notably the cerebellum (19), for "it make no great part" of his account of the motor cortex and the pyramidal tract (14).

Let experiment have frozen proper activities of servo-mechanisms by fixing bones, muscles, joints, etc., then excitation of one or few Betz cells will evoke what Jackson called movements (16), that is to say contraction of few muscles (20) and, perhaps, relaxation of antagonists—a complexity not allowed by the classical description of the motor cortex as a harpsichord with a cell to pluck each string (21, 22, 23, 24). No better is Wishe's notion (25) that these cortical efferents, like the push buttons of some monstrous "juke box", serve each to evoke entire some innate or learned "pattern of movement", (26, 27) which dwells in one such efferent at least and is not else effectable (27).

These inept conceits—accordion, harpsichord and juke box—like failed to predict the disparate consequences of stimulation at diverse frequencies (28). Percival Bailey has shown us that from all parts of Face Area 4, where twelve or more impulses per second regularly evoke contraction of facial muscles innervated by the seventh nerve, ten or less per second elicit only movements of the tongue, innervated by the twelfth alone (29). As he excited the efferents directly, and impulses descending conserve frequency (30), only filters in lower structures accomplish their diversion.

In familiar phrase, we might concede that frequency as well as place must enter our "idea" of the mode of representation of motion, and conceive the cortex an English horn. This opinion, as sweet, equivocal and perfidious as its three precedents, is as legitimate. For the lexicographer (31) will allow all four, and twenty others like them, quite impartially, each with a good sense of "to represent." All are metaphorical, compatible, assert little, predict nothing. It were less deceptive to have cortex

"represent" that internuncial ocean where its axons end—better, to do nothing of the kind (32)

Now nothing from the cortex partakes in the functional organization of the cortex unless the recipient internuncials affect the cortex again, and only so much as the corticofugal activity informs the return. We shall treat such feedback under Indirect Functional Organization, merely remarking that the cortex does thus affect its sensory input (33, 34)

The number of corticopetal fibres has been variously estimated, but I can find no one but Earl Walker brave enough to make it a hundred million, even in man. From the relative density of thalamic to extrinsic cortico cortical fibres we may admit of the latter as many more, i.e.  $10^3$ . The number of cortical neurons to be connected we may likewise round off at  $10^{10}$  again in man (35). Thus indirect and extrinsic fibres together are no more than a fiftieth of the associators of cortical events, for we can estimate the actual number of intrinsic cortico cortical axons by recalling that less than one in a hundred leaves the cortex. Thus gives us again a hundred intrinsic to one extrinsic and one indirect cortico cortical connection. To the ramification of axons we look for the multiplication of synapses required for summation.

We turn, therefore, to the grey mass of the cortex. Histological pictures by Cyral (36) and Lorente de Nó (37) show we can separate its vertical from its horizontal constitution. Conceive, then, the cortex as a mass of cells, say a hundred in depth (38, 39), divisible into ill defined layers containing principally neurons of given kinds, so connected from layer to layer that there are skip distances of one layer in their vertical synapses except in the outermost and innermost where cells of the odd and even series associate (37). In the intermediate layers are chiefly neurons whose axons are vertical with only subsidiary horizontal ramifications. Such vertical systems of neurons can reverberate (39, 40, 41) longer than if all layers were equally thoroughly interconnected by single axons. They can easily tolerate rhythms whose period is determined by a full circulation through the hundred cells, for this, with reasonable allowance for slow conduction and synaptic delays demands but ten impulses per second in each neuron. And we know some neurons that fire for long periods at twenty times that frequency (42-43).

Yet, it has become increasingly evident that this rhythm usually recorded from idle cortex may not be attributable to it alone (44-45) but rather to its ability to follow without loss that frequency imparted to it by unspecific afferents from undifferentiated thalamic structures (46, 47, 48, 49, 50, 51, 52). As yet there is nothing to suggest that it is anything more than a happy coincidence of the natural periods of intrinsic and indirect functional organizations, which may become unhappy when

three per second impulses appear (53, 54), leading to *petit mal*, with its spike and dome (55) that block all proper function of cortex and thalamus (56). These gross fluctuations of voltage through the cortex, having properties largely dependent simply on distance, resemble all disorders which introduce "fields" (57, 58, 59), be they physical or chemical or both, into mosaics of cells each capable of a discrete decision—impulse or none—and thereby consume the effective degrees of freedom without contributing to the precise ordering of their decisions, that is, to information (60). In 1936 Bishop showed that even the mild fluctuations, or alpha rhythm, of idle brain have a somewhat similar effect (52).

To him we are yet more indebted for the first proof of any function of the largest single huddle of extrinsic cortico cortical connections, the corpus callosum, for he showed that, on cutting the visual cortices loose from the geniculate bodies, it swept them into phase (52). Van Wagenen and Akelaitis (61, 62, 63, 64, 65, 66) have proved its unimportance by exhibiting the relative normality, including the continuity of visual perception (65), after its section in epileptics, in whom the section frequently prevented spread of grand mal convulsions across the midline. Its ability to sweep the other hemisphere into such seizures, Erickson proved (67), and I can confirm, with all paths through lower structures interrupted. Had Van Wagenen included the anterior commissure in his transections probably all his operations would have succeeded (68). Although I have spent much time synchronizing one square millimeter of cortex in primates under Dial and recording the impulses over the extrinsic system (69), I for one am convinced that although it alone can keep the cortex promptly informed of its own remote activity, no more specific task can yet be surely ascribed to any part of it. To generalize convulsions is scarcely its duty. Our inability to discover its role is exasperating, for with  $10^{10}$  neurons organized vertically by hundreds, there are some  $10^3$  such vertical groups and hence nearly enough extrinsic axons for one to go to each group.

But before we return to these groups whose numbers and arrangement ultimately determine the cytoarchitecture of the cortex let me say that Buley and von Bonin have completed their study of this aspect of *Macaca Mulatta* (70) and are well along on *Pan Satyrus* (71), that histological facts have compelled them to adopt von Economo's cyto-graphy (35) and that all our neuronographic findings on these extrinsic connections when so plotted show regularities we sought in vain in Brodmann's scheme (72). Sooner or later we shall adjust nomenclature to the medueable vertical structure of the *cortex cerebri*.

We have seen that this structure could support rhythms requiring say 100 synaptic delays—but we know that the time for reflections through the



thick of the cortex is often less than 10 synaptic delays (52, 73, 74) with due allowance for conduction. An incoming volley of specific afferents initiates a surface position wave of say 2 milliseconds (52). This is followed by 4 or more milliseconds of surface-negativity (52) while it inhabits and spreads in superficial layers. Then it descends, taking perhaps 2 more milliseconds (52). A primary sensory area bombarded by such afferents properly timed at lower levels might then be driven at 120 cycles per second, if output and input did not interfere. Presumably they do, for its highest recorded frequency is that at which flicker fuses, about 53 per second (75, 76, 77, 78). Now there can be but one corticofugal fibre for the whole 100 cells of which some or all have come into play to determine, in a matter of say 5 synaptic delays, whether that efferent shall fire or no.

The maximum information (60) that may enter such a decision of the corticofugal fibre in this short time is the time in synaptic delays multiplied by the number of neurons, i.e.  $5 \times 100$ , or as much information as can be conveyed in twenty five lettered words. Since these neurons are arranged in reverberating chains (39, 40), a second impulse, following a first within any period during which their reverberations are still informed by the first, has a fate determined in part by that active memory (78). Moreover, these columns are not merely linked with remote columns by one extrinsic fibre, but with adjacent columns by numerous fibres (39, 40, 79) and with others in the neighborhood by fewer, the number decreasing with increasing distance. Thus, the information brought to bear in determining the twenty words-worth of information is many times more. It increases with the duration of a figure in the impinging world, and all our perceptions of tone, chords, positions, shapes, etc. become blurred (43, 80) when one figure of excitement succeeds another at say 10 per second.

This demands a process which shall, from information radiating through the cortex out of the many channels that report the world, abstract one or more universals, or ideas (81). These may be found by scanning the recipient volume of cortex to discover figures of excitement regardless of position or size. To scan that space we shall detect and relay to fixed points the coincidence of the information with a horizontal plane of excitement that sweeps up and down the volume. Let it step but a cell's height per synaptic delay, and the time for clear perception, be it form seen or chord heard, becomes the required tenth of a second. Large electrodes on a cortex uninformed detect the sweep of scansion (82, 83), but on a cortex informed, the sweep is lost in the twinkle of details comprised in the perception (82, 83).

This fancy cleaves to fact, prescribes experiment, predicts outcome, invites refutation. It does not

strain credulity, for more statistical order suffices for nets to embody this process, inasmuch as small perturbation of threshold, of excitement, even of synapsis has little or no effect on the average that is the figure, or idea. These nets are random in detailed synapsis, for genes do not predetermine termini to all neuronal ramification.

If connections in the felt work of the cortex be random they are suitable to explain that surface negative wave which expands in a circle about a mildly stimulated point in the cortex. Rosenbluth measured its rate of propagation from a strychninized spot under chloralose (84). The circle expands too slowly to be spread by anything but repeated synaptic relay. It diminishes as it spreads. But weak strychninization of an area near its origin renders that area hyper excitable and then radial symmetry is lost, for the wave, with greater size and steeper front, races across the strychninized area (85). I could make little of this until Walter Pitts set up the mathematics for conduction in the random net (86). Now it appears as a verification of his theory that its velocity of propagation is determined by the rate at which spatial summation reaches a critical value in a random net and, therefore, by the threshold of the cells.

We have theories now that will force us to many experiments that may reveal to what extent the nets of the cortex are ordered, but none that will account for the ordering of these nets by learning, for this, like crystallization, is a change of state, and for such stochastic processes the mathematics is not yet (87, 88).

In closing, let me rehearse the general order that can be seen. Sectors of cortex, defined by their connections with thalamic nuclei (89), severally exhibit a receptive area or a pair juxtaposed but oriented reversely (90, 91, 92) each surrounded by a zone to which it gives many extrinsic axons. From each of these composite fields arises a projection whose activity affects that part of the body in which its organs of sense are situated. Thus the *area striata* (93) and its surrounding zones (94) move the eyes toward the place in the visual field corresponding to the position of excitation. The first and second somesthetic areas and the zone anterior to the former and deep to the latter (95) in the Sylvian fissure, extending on to the Island of Reil, direct the carriers of their appropriate receptors, and the superior surface of the second temporal convolution pricks up the ipsilateral ear (96).

This close cortical coupling of each sensory input to output affecting that sensory input by moving the organ of sense is a mode of functional organization whose circuit leaves and returns to the body. It is more indirect than the interception of sensory impulses to cortex which area 4s achieves *via nuclei caudati* by blocking thalamic relay (97, 98,

99) Yet circuits through the external world are but extensions of what Bell proposed merely through muscles in The Nervous Circle. On these re-entrant activities Cannon founded his conception of homeostasis (9), and Rosenblueth and Wiener, their theory of purposive behavior (100).

In primates these appetitive circuits pervade the cortex wherein their dominance is ordered and

whence their dominion is effected. Yet the general plan of the cortex makes its own functional organization imperfect without control of input by output, over links beyond the present scope of physiology. They are to be sought wherever appetitive circuits traverse the public world. Unlike unicorns some of these links are always to be found in Parliament Square (101).

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*since the age of 18 years, starting with sensation in the left side of the body and progressing to clonus of the left arm and leg*

Following sterilization of the scalp, nupercaine in solutions of 1:1500 and 1:4000 was injected along the line of incision. Sterile towels were then sutured around the operative field and arranged so the patient could be constantly observed by the anesthetist. A right fronto-parietal craniotomy was then done and the dura opened widely, exposing the surface of the hemisphere. The exposed cortex was kept moistened throughout the operation with Ringer's solution, sprayed on with an atomizer. An electroencephalographic exploration of the cortex was next done and the areas of abnormal activity marked by small tickets, bearing letters, which were placed on the brain at the point of origin of the abnormal waves.

The cortex was then stimulated with bipolar electrodes with the points separated about 3 mm. Occasionally a unipolar stimulator has also been used. The current was supplied by a stimulator built by Rahm (25). This apparatus produces a saw toothed wave with a rising phase lasting a fraction of a millisecond. The frequency and voltage of the stimulation can be accurately controlled and varied independently. The stimulation is ordinarily started with a setting of half a volt and then increased to 1, 1½, 2 or 3 volts as is necessary to produce a response. The maximum voltage used has been 3 volts in the central region and 5 volts elsewhere. Prior to 1945, a thyratron was used which furnished pulses lasting a fraction of a millisecond. The usual frequency employed was 55 to 65 per second. Beginning with a subliminal stimulus, the strength was increased until positive responses were obtained. Because of the short duration of the pulses, considerably higher voltages were used, usually 10 to 30 volts, occasionally up to 60 or 70.

The Rolandic fissure was first outlined, each positive response obtained being marked by a small number which was placed on the brain and indicated the site and order of the positive responses. Any unusual response was verified by repetition before it was accepted. The remainder of the cortex was then explored with the strength of the stimulator current moderately increased, in an effort to reproduce the patient's aura. The details of the electrical exploration were dictated by the surgeon to a stenographer, present in the gallery, who recorded the number of the stimulation, the voltage and frequency used, a description of the response, frequently in the patient's own words, and the time. Life size photographs were taken of the brain with the tickets in place. At the end of the stimulation the surgeon sketched on a life size standard brain chart any gross lesion that was present and entered the numbers at their proper measured distances from the Rolandic, Sylvian and median longitudinal fissures.

#### METHOD OF ANALYSIS

As in the previous analysis any movement or sensation which was part of an epileptiform seizure, however minor, was excluded. In addition, responses which were the result of widespread epileptic facilitation were eliminated (23). After analyzing the sequence of the responses in the record, the points for each individual bodily unit were transferred to full size standard charts of the corresponding hemisphere according to the measured distance on the operative photographs and charts from the Sylvian, Rolandic and median longitudinal fissures. A series of charts were thus compiled, each presenting the points which produced sensation or movement in one part of the body. The points from both hemispheres were then transferred to similar charts of the right hemisphere for purposes of summary.

Special analyses were made of records giving specific information on 1) the banks of the pre- and postcentral gyri within the Rolandic fissure, 2) the medial surface of the hemisphere, 3) bilateral and ipsilateral responses, 4) the question of the sensory representation of the pre- and postaxial surfaces of the extremities, 5) the question of the separation of the cortical representation of the primitive flexor and extensor muscle groups, and 6) a possible second sensory area.

#### SENSORY RESPONSES

*Cortical areas involved.* Sensory responses were elicited primarily from the cortex adjacent to the central fissure. In the face area, 82 per cent of the sensory responses were postcentral and 18 per cent were precentral. In the arm and leg areas, 73 per cent were postcentral and 27 per cent were precentral. The ratio of pre- and postcentral responses varied considerably among the various units of the sensory sequence. Sensation in the eyes and intra-abdominal sensation were located almost exclusively in the precentral gyrus, while sensation in the lips was nearly as completely limited to the postcentral gyrus. The sensory responses for face, arm, leg, foot and toes were divided more equally, 60 per cent postcentral and 40 per cent precentral. The majority of these responses were located adjacent to the fissure, but an appreciable number were situated in the anterior portion of the precentral gyrus or posterior portion of the postcentral gyrus. Rarely were sensory responses encountered at a distance greater than 1 cm. from the central fissure.

The sensory projection area in primates as mapped out under anesthesia by the method of evoked potentials (5) (29) does not extend onto the precentral gyrus and is limited to areas 3, 1 and 2. As mapped out by the method of local strychninization (11) the sensory area seems to extend much more widely both rostrally and caudally from the central fissure.

There is great variability in the location of the sensory leg area with respect to its extension onto the lateral surface of the hemisphere. Sensation in the foot and toes has been elicited from the lateral surface of the hemisphere near the midline, while at the other extreme the trunk area has been found to extend up to the midline and onto the medial surface of the hemisphere so that in one patient the uppermost stimulation on the medial surface of the hemisphere produced sensation in the lower trunk extending into the leg.

**Combined responses** In the majority (70 to 85 per cent) of the stimulations with these minor threshold currents sensation limited to one of the units listed in the sensory sequence was produced. In the remaining stimulations sensation was produced in two or more of these bodily units or movement was produced in addition to the sensation. Detailed examination shows that the great majority of these combined responses involved adjacent units in the sequence. Much more rarely the associated phenomena involved a more distant component of the same primary subdivision of the sequence. Responses involving the face and arm area, or the arm and leg area, were very rarely encountered. The face, arm and leg areas act as units when studied by local strychninization (11). A functional separation between these areas is also indicated by the rarity of cortical stimulations producing sensation in units separated by these boundaries. These responses, occurring among about a thousand sensory responses, are listed below.

**Responses involving the face and arm areas** 2 stimulations—sensation in mouth and thumb, 1 stimulation—sensation in face and index finger, 1 stimulation—sensation in tongue and index finger, 1 stimulation—sensation in roof of mouth, side of face and fingers, 1 stimulation—sensation in face and ipsilateral side of chest with trembling of lips.

**Responses involving the arm and leg areas** 3 stimulations—sensation in arm and leg, 1 stimulation—sensation in arm and a little in the foot, 1 stimulation—sensation in hand and foot, 1 stimulation—sensation in hand, arm and foot with tremor of arm and foot.

As might be expected from the small size of the trunk area, responses involving the trunk and the arm or leg were relatively more frequent.

**Responses involving the trunk and the arm or leg areas** 5 stimulations—sensation in arm and trunk, 1 stimulation—sensation in arm, body and foot, 3 stimulations—sensation in back and leg, 1 stimulation—sensation down the entire left side of the body, shoulder to foot, 1 stimulation—sensation down the left side of the body from umbilicus to knee, 1 stimulation—sensation down the left side of the body, into leg with flexion of the knee.

The paucity of these responses is to be contrasted with the combined responses within the

principal subdivision of the central area. For example, 20 (11 per cent) of the 112 tongue responses showed associated sensation in neighboring units of the sequence. Similarly 25 (26 per cent) of the 97 thumb responses, 31 (14 per cent) of the 214 hand responses and 30 (30 per cent) of the 100 arm responses were combined responses.

The sensory cortex is thus apparently organized so that various bodily regions are represented in an orderly, constant manner with, however, a variable degree of overlapping so that at any one spot on the sensory cortex there is represented a functional unit pertaining to some region of the body, and possessing a low threshold to electrical stimulation. Into this same area, however, extend functional units related to neighboring portions of the body and exhibiting higher thresholds. This overlap is most marked in the area for the digits of the hand and is least marked at the junctions of the face, arm and leg areas. The degree of this overlap has been well demonstrated by the evoked potential studies in experimental animals (20).

**Bilateral and ipsilateral sensory responses** Bilateral and ipsilateral sensory responses occurred only in the face area. The incidence of these responses varied considerably in the different units of the face area, but they occurred in nearly all. Half the sensory eye responses consisted of sensation in both eyes simultaneously, in the other half the sensation involved only the contralateral eye. Eight per cent of the total group of sensory responses in the face area (13 per cent of those in which the lateralization was described) were either clearly bilateral or ipsilateral.

These bilateral and ipsilateral sensory responses were situated in their expected location in the sensory sequence of the individual patient and were frequently adjacent to usual contralateral responses involving the same part. The character of the sensation was also the same as in the ordinary contralateral responses. A discrete cortical area related to the ipsilateral side of the face has not been identified by cortical stimulation in man. On the other hand in experimental evoked potential studies such an area has been outlined for the pig, sheep, rabbit, cat, dog and monkey (34). Adrian found ipsilateral evoked potentials from the face in the goat and sheep and only contralateral responses in the pig, ferret, Shetland pony, cat, dog and monkey (2) (3) (4).

#### MOTOR RESPONSES

**Cortical areas involved** Movement of the various parts of the body were produced primarily from stimulation of the precentral gyrus adjacent to the central fissure and less frequently from stimulation of the adjacent part of the postcentral gyrus. The percentage of responses elicited from the postcentral gyrus varied from unit to unit within the

motor sequence. In the case of neck movement, movement of the eyelids, eyeballs and brow, all the points were precentral in location. Mastication, on the other hand, was located mainly in the postcentral gyrus. For the remainder of the face area, 28 per cent of the responses were postcentral, as were 21 per cent of the motor responses of the extremities. In the chimpanzee, also, discrete motor responses have been elicited from the postcentral gyrus as well as from the precentral gyrus (12) (17).

One third of the points for eyeball movement were located adjacent to the central fissure while the remaining two thirds were in the anterior part of the precentral gyrus or in the general vicinity of area 8. The ratio was just reversed for eyelid movement, two thirds of the points being adjacent to the central fissure and one third further anteriorly. Contraversion of the head did not occur as a result of stimulation adjacent to the central fissure and all the points were located in the anterior margin of the precentral gyrus and in the region just anterior, corresponding in general to area 8. Neck movements other than those producing contraversion of the head were localized at the precentral margin of the Rolandic fissure.

While the great majority of the responses in man were located adjacent to the central fissure, occasional points were present in the anterior portion of the precentral gyrus or the posterior portion of the postcentral gyrus, and rarely were situated in the next gyri anteriorly and posteriorly.

Motor responses were elicited in 13 of the 15 operations in which the banks of the Rolandic fissure were stimulated below the outer or superficial surface. These occurred both from stimulation of the pre- and postcentral gyri. As with the sensory responses these motor responses were comparable to those elicited from the outer surfaces of the gyri and were located at the proper site in the motor sequence mapped out by the surface stimulations in each individual patient.

The relative size of the motor face, arm and leg areas varies considerably. The face area may extend to within 4 cm. of the midline, or at the other extreme the face area may be so small that thumb responses are elicited 2 cm. above the fissure of Sylvius\*. A similar variability exists for the leg area. It may be entirely located on the medial surface of the hemisphere or it may extend well out onto the lateral surface for a distance of 3 cm. Flexion or extension of the ankle were elicited 13 times by stimulation on the lateral surface of the hemisphere and on 2 occasions toe movements were produced here.

*Sequence.* Only minor changes were made in the motor sequence previously described (fig. 1). Vo-

calization has now been elicited throughout the lower face area of both the dominant and non-dominant hemispheres and does not seem to be sharply localized within this region. It occurs both alone and in association with movement or sensation of units of the lower portion of the face area. Mastication has a separate representation from other jaw movements. It is apparently represented primarily in the postcentral gyrus, in the region of the sensory tongue area and below. The simpler jaw movements, on the other hand, were found to be located primarily in the precentral gyrus and above the motor responses for throat and tongue. Mastication was therefore added to the motor sequence below throat and tongue. Salivation was found in the same region as mastication, in the postcentral gyrus, and was added to the motor sequence here also.

Eyeball movement was inserted into the sequence with eyelid movement, since as stated above, one third of the responses were located in the motor strip adjacent to the central fissure just like motor responses for other units of the body. They were consistently found between face and thumb.

*Representation of flexors and extensors.* No evidence was found to suggest that the muscles derived from the ventral muscle sheet of the limb bud (the primitive flexors) were separated in their cortical representation from those derived from the dorsal muscle sheet (the primitive extensors) (Woolsey) (25). Flexion and extension of the same joints were occasionally produced from closely adjacent points. Also no leg movements were produced above foot and toe movements in the motor sequence. It seems likely that the demands of function have brought about an arrangement in the cortex so that agonists and antagonists are closely associated, thus producing the motor sequence classically described for man.

*Type of movement produced.* Movement of the great toe was rarely produced alone, flexion, extension or separation of all the toes occurred more frequently. Flexion or extension of the ankle, knee or hip occurred both alone and with more widespread movement of the leg.

Motor trunk responses occurred only 4 times, being clearly contralateral in 1 patient and not described in the other 3 in sufficient detail to make clear the lateralization of the response. Neck movements (except head turning) consisted of retraction of the head, contraction of the sternomastoids or trapezius and were represented between fingers and face, as judged by the 12 motor responses that were obtained. It will be recalled, however, that in the sensory sequence neck sensation was placed between arm and trunk along with head sensation.

Contraversion of the head was nearly always as-

\* Extreme variations may be the result of localized cortical atrophy produced early in life.

sociated with conjugate deviation of the eyes to the opposite side. The majority of the points for contraversion of the head were located anterior to the junction between the arm and face areas. This special mechanism is represented separately in the cortex from other neck movements.

The most common response in the arm area was movement of all the fingers together, but flexion or extension of the thumb was fairly frequent and movement of one of the fingers was elicited occasionally. Multiple finger responses were seen only in consecutive digits. Flexion and extension of the wrist and elbow were elicited frequently while shoulder movements occurred somewhat less often. The most common shoulder movements were elevation, inward rotation and flexion.

Flexion responses were in general more frequent than extensor responses. Many combinations were encountered, finger movements occurring most commonly with wrist movements, less commonly with elbow movements, and occurring with shoulder movement only as part of a movement involving the whole arm. Flexion of one joint sometimes occurred with extension of an adjacent joint. A flexion response occasionally occurred immediately adjacent to a point which produced extension of the same joint or joints. When sensation accompanied a motor response it usually involved the same part, but occasionally it occurred in an adjacent structure, i.e. flexion of the elbow with sensation in the hand.

The eyeball movements elicited from the anterior portion of the precentral gyrus and further anteriorly consisted almost exclusively of rotation of the eyes to the contralateral side, with an additional upward or downward component in occasional instances. The eyeball movements elicited from the precentral gyrus immediately anterior to the central fissure, on the other hand, exhibited rotation to the ipsilateral side nearly as frequently as rotation to the contralateral side, and, in addition, upward rotation and convergence were occasionally produced. Experimental work has given some indication of localization within the frontal eye fields (10). This literature has been recently summarized by Smith (26).

Our studies show that the most frequent eyelid movement was closure of the eyes. The next most frequent response was twitching or trembling of the eyelids and the least common was opening of the eyes, possibly because the eyes were usually open at the time of the stimulation. Usually the response was bilateral but purely contralateral responses did occur.

Under face movement are included those responses consisting of contraction of the upper and lower facial musculature. A bilateral movement occurred once and an ipsilateral response occurred in a second patient, all the remaining responses

being contralateral. Lip movement was the most common of all the sensory or motor responses in the face area (160 stimulations) and they were mainly contralateral (107 stimulations). There were 16 bilateral responses and 2 ipsilateral. Opening of the jaw was the most common jaw movement produced, clonic twitching occurring about half as frequently, while closure of the jaw and pulling of the jaw to the contralateral side occurred still less frequently. In one instance the jaw pulled to the ipsilateral side. Tongue movements were usually retraction, protrusion, or twitching. Doubtless small movements of the tongue frequently escaped detection due to difficulties of observation. Throat movements were either swallowing or gagging. Masticatory or chewing movements were frequently associated with sensation in the tongue, roof of mouth, or throat, but also occurred alone.

These facial motor responses are more discrete than the better organized movements produced by stimulation in the lower animals. The transition as one ascends the animal scale from rat to the higher primates has been described by Walker and Green (27).

Cortical stimulation gives definite evidence of some bilateral representation in the motor face area in man. The relatively slight motor deficit produced by ablation of face area of the precentral gyrus in man suggests that the bilateral representation is more complete than in the stimulation data would indicate. Bilateral representation in the face area of the monkey has been studied in detail by Green and Walker (15).

In a recent patient, stimulation (2 volts, 60 cycles per second, bipolar electrodes) at one point in the leg area, immediately anterior to the central fissure, repeatedly produced abduction and extension at the hip in both legs. This may be analogous to the bilateral motor responses of the extremities reported in primates by Bucy and Fulton (7) and by Wyss (35). Aside from this isolated instance, however, there have been no ipsilateral motor responses involving the extremities.

The difficulty in accurately describing in terms of muscular action the movements produced by cortical stimulation in human patients limits the detail with which we can discuss the way in which the motor cortex in man brings about a voluntary movement. More detailed studies of stimulation of the human motor cortex are necessary for correlation with the results of experimental stimulation of the motor cortex in the laboratory. Most of these latter studies have utilized minimal currents (6) (12) (14) (9) (17) (18) (19) (27), but recently maximal subconvulsive currents have been employed (21). The accumulation of careful



studies of controlled ablations in man (8) is an important addition

#### SECOND SENSORY AREA

The constant presence of second sensory areas in all species of experimental animals thus far studied by the method of evoked potentials (1) (2) (30) (31) (32) makes it probable that such an area is also present in man. A survey of over 350 stimulation records has revealed 8 patients in whom the presence of such an area in man would

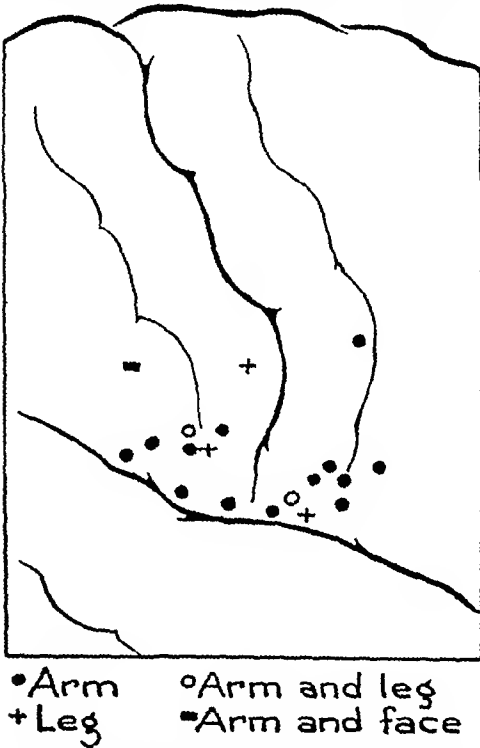


Fig 2 Diagram of the central region of the right hemisphere with summary of stimulations suggesting the presence of a second sensory and motor area in man

explain unexpected responses for which there was previously no explanation. Some of these were mentioned briefly, by one of us (W P), in the Ferrier Lecture for 1946 (24). These data are presented in this tentative light since we do not feel that sufficient information on this point is available yet for a more positive statement on the presence of such a second area in man.

In all these 8 patients, the responses were elicited from the foot of the sensorimotor strip, just above the fissure of Sylvius (fig 2). In 3 patients, the area in question was in the precentral gyrus, in 3, it was in the postcentral gyrus, and in 2, it involved both. There were 19 responses in

these 8 patients. Fourteen were sensory responses, 2 were motor and sensory, and 3 were motor. The sensory and motor responses were equally distributed as far as lateralization was concerned: 8 were contralateral, 2 were ipsilateral, and in 9, the lateralization was not stated. Thirteen involved the arm, 3 the leg, 2 the arm and leg, and 1 the mouth and arm. The distal portions of the extremities were primarily involved, two thirds of the responses being referred to the hand or foot, one sixth to the digits and the remaining one sixth to the arm or leg. In 6 patients the right hemisphere was stimulated and in 2 the left. The sensations produced were described by the patients in terms similar to those used to describe sensation produced elsewhere throughout the central area.

In view of the presence of motor responses in this area as well as sensory phenomena it is of interest to note that Garol (14) identified a second motor area in the cat in a location that corresponds closely with the second sensory area mapped out by Adrian (1) and Woolsey (31) (34).

#### SUMMARY

1 As a result of further stimulation studies in man, certain modifications in the sensory sequence are suggested: (a) The head as a whole is represented between trunk and arm. (b) Neck sensation seems to belong between the head representation and trunk. (c) Tongue sensation has been moved to below teeth, gums and jaw, conforming to its location in the motor sequence. (d) Taste has been eliminated from the sequence of the cortical convexity since it occurs very rarely as a result of stimulation here, although somatic sensation in the tongue is the most frequent sensory response in the face area. (e) Intra-abdominal sensation has been added to the lower end of the sequence, below throat. The extent of this representation, which is largely precentral, into the island of Reil has not yet been determined.

2 Sensory responses simultaneously in more than one of the area units of the face region are fairly frequent. The same is true among the units of the upper extremity. It is, however, very rare that overlap occurs between the three major regions—face, upper extremity, lower extremity. This may cast light on the fact demonstrated by Dusser de Barenne and McCulloch (11) that each of these regions may be activated in animals by local application of strychnine without activating the adjacent major region.

3 Stimulation of the banks of the Rolandic fissure have shown that the sensory and motor responses produced there are similar in character and location to those elicited from the superficial surfaces of the pre- and postcentral gyri.

4 In the motor sequence certain minor alter-

ations are also suggested (a) Salivation and mastication are represented in the lower portion of the motor face area. The latter is predominantly postcentral in location and below tongue, whereas simple jaw movements are predominantly precentral in location and located above tongue (b) Neck movements are represented between the area for finger movements and the upper margin of the face area

5 Vocalization may be produced in man from an area between upper face and throat of both the dominant and non dominant hemispheres, either alone or with movement or sensation in the various structures about or in the mouth

6 Conjugate eye movements toward the opposite side are produced by stimulation anterior to the precentral gyrus without seeming to be confined to a discrete architectonic area. Eye movements produced from the precentral gyrus may be conjugate to either side or upward, or may be movements of convergence. Eye sensation is produced by stimulation anterior to the central fissure but not posterior

7 Evidence is presented for the possible existence of a second sensory area for arm and leg in the cortex adjacent to the fissure of Sylvius. It seems likely also that there may exist in the same zone a second representation of movement

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JOINT SESSION OF THE FEDERATION  
Chicago, May 19, 1947A BAIRD HASTINGS, *Chairman*  
*Harvard Medical School*

## SYNTHETIC PENICILLIN\*

VINCENT DU VIGNEAUD

*Department of Biochemistry, Cornell University Medical College*THE CONDITIONS ASSOCIATED WITH THE SECRETION  
OF THE ADRENAL CORTEX

C N H LONG

*Department of Physiological Chemistry, Yale University*

The science of endocrinology is developing in a manner paralleling that of its sister sciences. That is to say, from a beginning as merely a description of the phenomena attending the loss or an excess of an internal secretion, it is passing by slow degrees to a study of the manner by which these secretions regulate the metabolic processes of the cells upon which they act. It cannot be too strongly emphasized that the hormones do not initiate new types of cellular activity but only influence the rate at which these functions proceed. Since it is now recognized that cellular function is based on underlying chemical transformations, it may be assumed that all that any hormone does is either to facilitate or retard certain types of chemical reactions within cells. However, the actual manner by which such acceleration or retardation is effected remains, with one exception, extremely obscure. This exception is the report by Price, Colowick and Cori (1) that an anterior pituitary hormone and insulin exert at least part of their physiological action by regulating the rate of the hexokinase reaction.

It is evident, however, that the future development of endocrinology will be inextricably combined with and dependent upon the growth of our knowledge of the intermediary metabolism of the cells. Indeed, it is fair to suggest that "biochemical endocrinology" offers at the present time the most promising field for the elucidation of the exact nature of hormonal action.

This afternoon I am venturing to speak to you on certain biochemical studies that have been carried out in recent years both in my own and other laboratories which may offer not only an illustration of the generalization I have just stated but also I hope will add something to our knowledge of the conditions associated with the activity of

one of the most vital of all endocrine organs, the adrenal cortex.

There are three main goals that must be reached for an understanding of the role played by any endocrine gland and its secretions in the regulation of the economy of the organism. They are (1) The isolation, determination of chemical constitution and if possible, the synthesis of the active principle or hormone, (2) The recognition of the manner of interaction of the hormone with the cells upon which it exerts its effect. This, as I mentioned above, may ultimately prove to be the positive or negative catalysis of some particular chemical transformation carried out by the cell. (3) Since the hormones are to be regarded as one means by which the functions of the organism as a whole are correlated and integrated one with another, it is desirable to know the circumstances under which a heightening or lowering of the rate of secretion of the constituent members of the endocrine system occurs. Such information, particularly if we can establish the nature of hormonal action, would contribute to our understanding of the way in which the organism responds and adjusts itself to the continued and varied alterations in its external and internal environment and would indirectly give a clue to the cellular processes that are essential for the fulfillment of such adaptations.

The determination of the manner by which any endocrine organ is able to augment its secretion, demands for its solution, first an understanding of the circumstances associated with such secretion and, secondly, a knowledge of the mechanisms by which the increased quantity of hormone is produced by the secretory cells of the gland.

THE ADRENAL CORTEX-ANTERIOR  
PITUITARY RELATIONSHIP

Before describing those experiments that relate particularly to the conditions of activity of the

\* This paper will be published later.

# THE EFFECT OF ADRENOTROPHIC HORMONE UPON THE ADRENAL CHOLESTEROL

The injection of purified adrenotrophic hormone (A C T H) essentially free of all other anterior lobe hormones in quantities of 1-4 mgs into normal rats, mice and guinea pigs is followed by characteristic changes in the content of cholesterol in the adrenal glands. These consist of a sharp initial decline reaching a maximum some 4-6 hours after the injection (figure 1). The extent and continuance of this fall is roughly proportional to the quantity of A C T H administered but the injection of the above-mentioned quantities of hormone results in the rat and mouse in the loss of some 50-60% of the original content within 3-6 hours

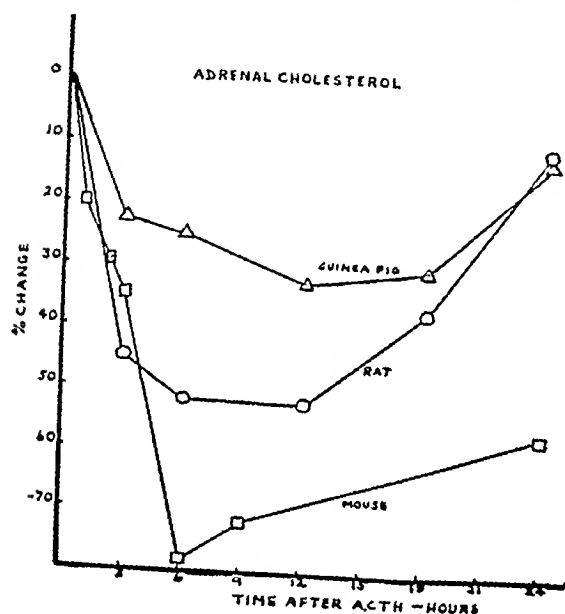


Fig 1 The effect of a single injection of adrenotrophic hormone (A C T H) on the adrenal cholesterol of the guinea pig, rat and mouse. From the data of Sayers, Sayers, Liang and Long (11) and Dougherty and White (10)

The content then slowly rises but may require some 24 hours to return to the initial level. Analysis indicates that the loss is almost entirely due to a decrease in the ester fraction, the quantity of free cholesterol remaining almost unchanged.

These changes in adrenal cholesterol under the influence of A C T H are not accompanied by similar declines in the cholesterol content of liver, spleen, brain, heart, lymph nodes, skeletal muscle or blood plasma. They may, therefore, be regarded as a specific response of the adrenal to the stimulus of the trophic hormone.

Hypophysectomized rats 3-14 days after operation have higher initial levels of adrenal cholesterol than normal rats yet respond in a similar manner to the injection of A C T H (6)

While there is at present no direct evidence that these changes represent the conversion of cholesterol into the characteristic adrenal cortical steroids, the indirect evidence that they are closely related to the actual formation and release of these hormones may be summarized as follows: (a) There is a close chemical relationship. (b) The work of Bloch, Berg and Rittenberg (7) and of Bloch (8)

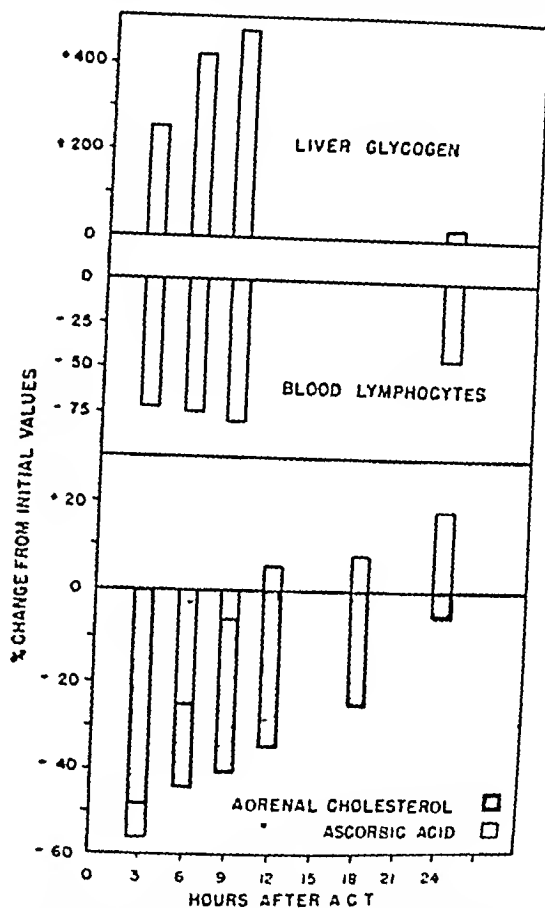


Fig 2 The changes in (a) Liver glycogen (b) Circulating Blood Lymphocytes and (c) Adrenal Cholesterol and Ascorbic Acid following a single injection of adrenotrophic hormone (6, 10, 11)

show that cholesterol is actually converted into cholic acid and into progesterone. (c) These effects of A C T H upon adrenal cholesterol are accompanied by definite physiological indications of an increased output of the cortical hormones. Thus, it has been shown that the liver glycogen rises, reaching a maximum between the 6th-9th hour after the injection of the trophic hormone while the lymphopenia, shown by White and Dougherty (10) to be another manifestation of increased adrenal cortical secretion, also reaches its maximum between the 6th and 9th hour (figure 2). (d) Finally it can be shown that these changes in adrenal cholesterol are almost entirely confined to the adrenal cortex (11).

It may therefore be concluded that the fall in adrenal cholesterol following the injection of A C T H is not only a specific response by this organ, but also is an indication that cortical hormone has actually been released from the gland. *It may therefore be used not only to detect the release of A C T H from the pituitary, but also to determine whether any particular set of conditions is associated with the activation of the anterior pituitary adrenal cortex mechanism.*

#### THE EFFECT OF ADRENOTROPHIC HORMONE UPON THE ADRENAL ASCORBIC ACID

When it became apparent that A C T H did specifically deplete the adrenal cholesterol we turned our attention to its possible effect on the adrenal ascorbic acid. Since the latter substance was also

initial level may be regained about 6 hours after the injection of A C T H in the quantities employed in these experiments. In the rat such injections ultimately bring about an actual increase in the ascorbic acid content so that 24 hours later not only has the gland increased in size by some 20%, but the concentration of the vitamin has also increased to the same extent. It is important to emphasize that no significant alterations in the ascorbic acid content of the blood or a variety of other tissues accompany these marked variations in the adrenal.

In the guinea pig a similar initial and prompt fall occurs, also reaching a maximum 3 hours after injection. From then on however the curve differs markedly from that in the rat since the return of

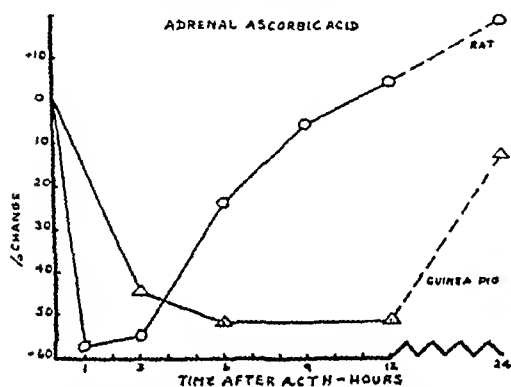


Fig 3 The effect of a single injection of adrenotrophic hormone on the adrenal ascorbic acid of the rat and guinea pig (11)

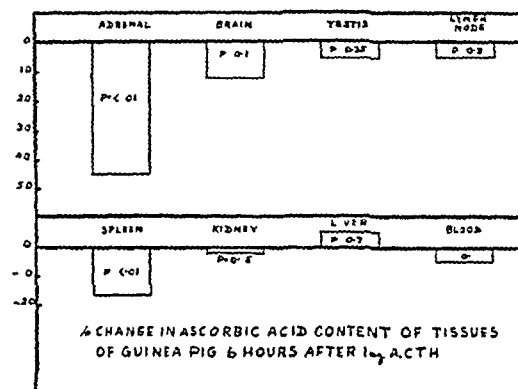


Fig 4 The effect of a single injection of adrenotrophic hormone on the ascorbic acid content of the adrenal and other tissues of the guinea pig (Oesterling — unpublished)

uniquely present in large amounts in this organ, it was in the first place selected as an internal control upon the specificity of the changes in adrenal cholesterol. Somewhat to our surprise it was found that this adrenal component also responded in a specific manner to the injection of the trophic hormone.

Up to the present time the response of the adrenal ascorbic acid to A C T H has been examined fully only in the rat and guinea pig. These two animals, however, represent species which can and cannot synthesize ascorbic acid and consequently it may be anticipated that certain aspects of their response to this hormone would be different.

As will be seen from Figure 3 a very prompt fall in adrenal ascorbic acid occurs in both species. In the rat a decrease can be found 20 minutes after the injection of A C T H while in 1 hour the gland may have lost 60% of its original content. This decline has, however, usually reached its maximum about 3 hours after the injection of A C T H and from then on increases again rapidly so that the

the ascorbic acid to normal levels is a slow process taking almost 24 hours for completion. This undoubtedly reflects the inability of this species to synthesize the vitamin and it may be presumed that the ultimate restoration of the original content is dependent upon the ability of the gland to replenish its stores from the blood since these animals received no vitamin C during the experimental period. The liver ascorbic acid and that of a variety of other tissues is unaffected. The only exception may be a slight fall in the spleen (figure 4).

In the *hypophysectomized rat* the adrenal ascorbic acid slowly declines with time after the operation (12). However, 2-3 days after operation the content is approximately that found in intact animals. At this point the intravenous injection of amounts of A C T H of the order of 1 microgram or less is followed by a rapid decline in the ascorbic acid. Indeed the adrenals of such animals are so sensitive to the trophic hormone that this procedure has been adopted by Sayers and Sayers (13) as a method of assay for A C T H.

While there are good reasons to believe that the adrenal cholesterol is the precursor of the adrenal cortical steroids, the relation of these changes in the Vitamin C content to the cortical secretion is not so evident. There is no apparent chemical relationship between the vitamin and hormone that might suggest its role as a precursor. There is, however, again a close parallel between the fall in ascorbic acid and the physiological changes associated with the cortical secretion. Furthermore, the effect of A C T H on adrenal ascorbic acid appears to be a specific one and as we shall see occurs in intact animals wherever the anterior pituitary-adrenal cortical mechanism is activated. Consequently it also can be used in the same manner as the changes in adrenal cholesterol for the detection

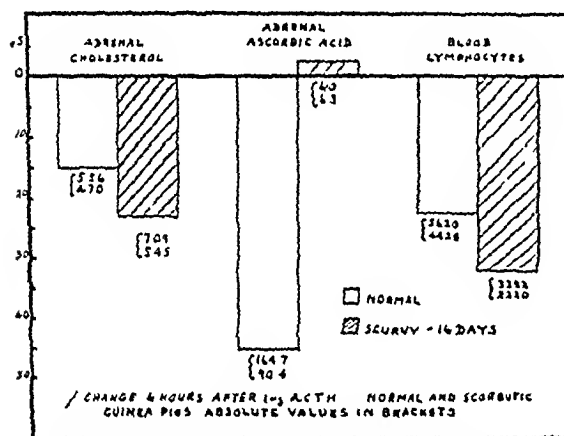


Fig 5 The effect of a single injection of adrenotropic hormone on (a) the adrenal cholesterol (b) the adrenal ascorbic acid (c) the circulating lymphocytes of normal and scorbutic guinea pigs (Oesterling — unpublished)

of the response of this portion of the endocrine system to changing conditions in the external or internal environment.

A recent note by Lowenstein and Zwemer (14) suggests that the cortical hormone is actually secreted by the gland as a complex of the steroid hormone and the vitamin. They claim that it is possible to isolate such a compound from the gland. While confirmation of the existence of such an adrenal cortical hormone would greatly clarify the association of changes in the vitamin and steroid content of the gland during active secretion, we have observed certain circumstances that suggest that the relationship between the steroid and vitamin is not as intimate as this work would imply. If guinea pigs are placed on a scorbutic diet, the adrenal ascorbic acid is, in the course of 14-16 days, reduced to about 40% of the normal value. At this time the adrenal cholesterol has increased some 20% over the value found in pair fed controls. The injection

of 1 mg of A C T H into such animals is followed in 6 hours by the usual fall in adrenal cholesterol and the development of lymphopenia. Nevertheless no further loss of ascorbic acid is observed since at this time to all intents and purposes the gland may be regarded as essentially free of the vitamin (figure 5). It is evident from this experiment that in the guinea pig not only is the fall in cholesterol following A C T H independent of that in ascorbic acid but also that it is still associated with the release of cortical hormone with its consequent effect upon the lymphoid elements. The response of animals suffering from more advanced scurvy has not yet been examined. In this condition, however, it is known that the adrenal cholesterol has declined to levels approximately 50% less than those found in the pair fed controls. It was not known whether these changes in the chemical architecture of the adrenal bear any relation to the clinical events associated with advanced scurvy although the possibility that adrenal cortical insufficiency may be present in this condition has been discussed by several groups of investigators.

In the rat similar indications of a dissociation between the movements of adrenal cholesterol and ascorbic acid have been observed. In these animals 24 hours after injuries, injection of bacterial toxins, or hemorrhage the adrenal cholesterol may still be found at levels less than 10-20% of normal while the adrenal ascorbic acid has returned to nearly normal levels. The inherent capacity of these animals rapidly to synthesize the vitamin is evidently not coupled with their ability to reform cholesterol at the same rate.

Since the adrenal medulla as well as the adrenal cortex contains appreciable quantities of the vitamin, it is necessary to inquire whether the observed changes in the whole gland reflect the secretion of epinephrine rather than that of the cortical hormones. Heard and Welch (15) in perfusion experiments on ox adrenals found that the appearance of epinephrine in the perfusate was accompanied by that of ascorbic acid and indicated that the latter probably operated as an anti-oxidant for the former. There are, however, good reasons to believe that the loss of ascorbic acid following activation of the gland by A C T H is in large part, at least, from the cortical tissue. These reasons may be summarized as follows: (a) Direct analysis of the dissected cortical tissue of rats and guinea pigs indicates that the loss of ascorbic acid after A C T H accounts for nearly the total amount lost from the intact gland. (b) Hypophysectomized animals do not suffer depletion of their adrenal ascorbic acid when placed under conditions which are known to evoke epinephrine discharge from the medulla. (This will be considered in more detail further on.) This is not due to a failure to secrete

epinephrine since it has been shown by Cope and Marks (16) that a normal discharge of epinephrine occurs from the medulla of hypophysectomized rabbits as a result of insulin hypoglycemia. (c) In spite of the absence of any effect of sympathetic stimulation on the ascorbic acid content of the adrenals of hypophysectomized animals, even though accompanied by epinephrine liberation, the glands of such animals promptly release relatively large quantities of ascorbic acid when stimulated by the adrenotropic hormone. (d) Adrenal transplants consisting entirely of cortical cells show a fall in their ascorbic acid content after injection of A C T H or exposure of their hosts to cold.

It is therefore concluded that these changes in adrenal ascorbic acid following their activation by A C T H reflect to a major degree changes in the con-

centration of the vitamin in the cortex rather than in the medulla and that in consequence they together with the contemporary changes in cholesterol may also be used as indicators of adrenal cortical activation. Nevertheless it must be stated that direct evidence for the conversion of adrenal cholesterol to adrenal cortical steroids is lacking and that at the present time the relation of adrenal ascorbic acid to the secretory activity of the gland remains wholly obscure. This, however, need not detract from the use of such determinations to follow the conditions associated with adrenal cortical activity since they appear to be a reflection of it. A few applications of this method to the study of certain endocrinological problems may already be noted. (a) It has been shown by Sayers and Sayers (13) that the response of the adrenal ascorbic acid of the hypophysectomized rat to A C T H may be used as a method of assay for the hormone. (b) By this technique they have also determined the A C T H content

of a single rat anterior lobe, a possibility we have confirmed. It may be estimated by this means that the rat anterior lobe contains approximately 1% of A C T H (figure 6). (c) The most promising use of this method in clinical endocrinology would appear to be the determination of urinary A C T H excretion in man, a procedure of potential value in the diagnosis of certain types of adrenal cortical and anterior pituitary disorders.

The use to which this method has been put for the determination of the conditions of adrenal cortical secretion will now be described.

#### THE EFFECT OF CONDITIONS KNOWN TO BE ASSOCIATED WITH ADRENAL CORTICAL SECRETION ON THE ADRENAL CHOLESTEROL AND ASCORBIC ACID

It now appears to be established that one of the effects of stress, whether arising within or without the organism, is an increased demand for cortical hormone. The reasons for this increased require-

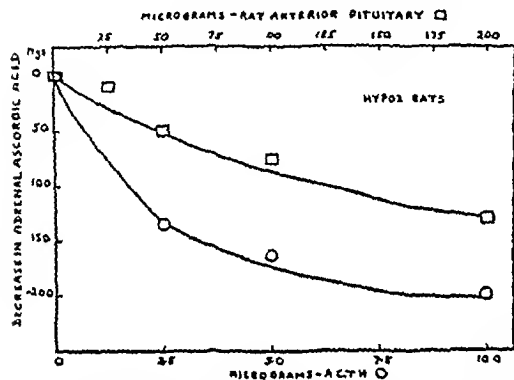


Fig 6 The effect of (a) adrenotropic hormone (b) saline extract of rat anterior lobe on the adrenal ascorbic acid of hypophysectomized rats. From data of Sayers and Sayers (13) and Long and Fry (unpublished).

ment are not understood, but presumably they are first met by an increased rate of secretion of A C T H. Indeed, in all discussions of this problem it must be clearly realized that the response of the anterior pituitary is not only the first but also the essential one in the events leading to adrenal cortical activation. The nature of the stimuli, whether nervous or humoral, that evoke this response are quite indefinite at the moment. Once the pituitary response has occurred, the adrenal cortex of a normal animal promptly responds by greatly increasing the output of its hormone.

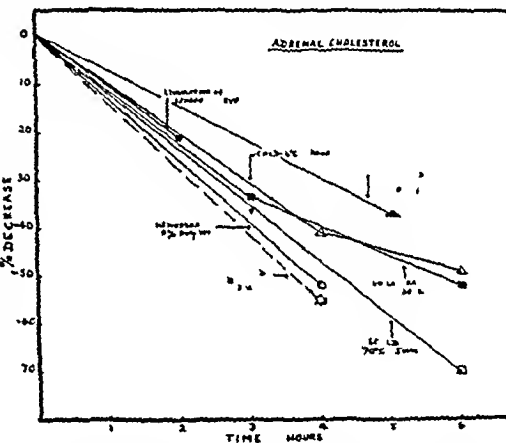


Fig 7 The effect of the exposure of rats to the conditions noted in the figure on the adrenal cholesterol. The data is from the following sources: Cold (22), Pain (22), Hemorrhage (23), Scald (24), Killed B Coh (Pinchot — unpublished), Unilateral adrenalectomy (Fry and Gershberg — unpublished), Simulated altitude (Tepperman — unpublished).

It is evident then that if the changes in adrenal



cholesterol and ascorbic acid following the exogenous administration of A C T H are a specific effect of this trophic hormone, then similar alterations in the composition of the gland should occur

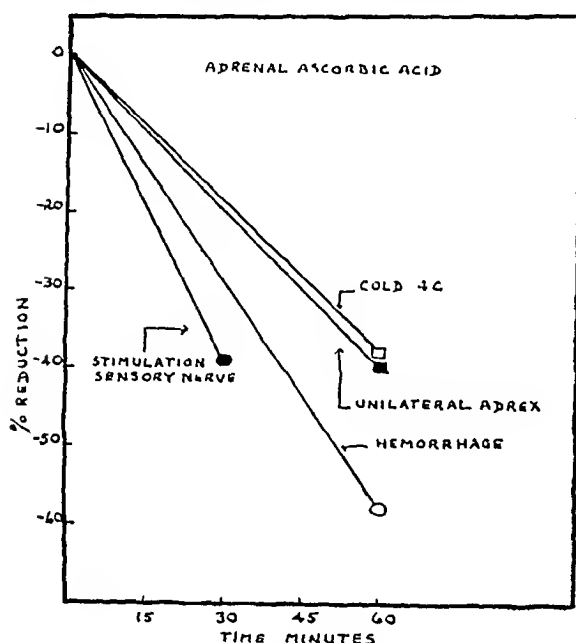


Fig 8 The effect of exposure of rats to the conditions noted in the figure on the adrenal ascorbic acid. For source of data see Figure 7

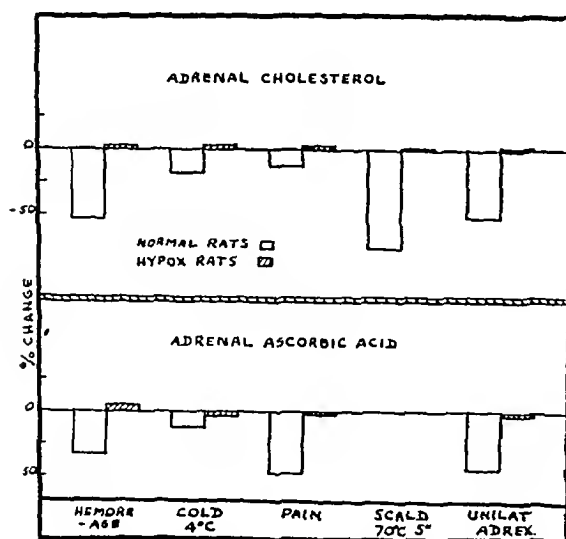


Fig 9 The effect of exposure to various conditions on the adrenal cholesterol and ascorbic acid of normal and hypophysectomized rats

when animals are placed under circumstances in which it is known that an increased secretion of cortical hormone is necessary for survival

Experiments of this kind under a variety of con-

ditions have been carried out by ourselves and others and the results are grouped together in Figures 7 and 8. It will be observed that following exposure of rats to (a) hemorrhage, (b) cold at 1-4°C, (c) scalds, (d) stimulation of sensory nerves, (e) operative procedures such as unilateral adrenalectomy, (f) injection of killed B. Coli, (g) simulated altitudes of 20,000 feet, that the adrenal cholesterol and ascorbic acid decline in a similar manner to that observed after the injection of purified A C T H. Similar treatment of hypophysectomized rats does not produce any significant change in these adrenal constituents even though the procedure employed may rapidly bring them to the point of death (figure 9). Indeed, the contrast in the response of the adrenal in those two groups of animals to the same circumstances leaves little doubt that not only does the cholesterol and ascorbic acid accurately reflect the release of adrenotrophic hormone but also that all adrenal cortical activity in the normal animal must first be initiated by adequate stimulation of the anterior lobe.

#### MECHANISM OF ACTIVATION OF ADRENOTROPHIC HORMONE SECRETION

The fact that such diverse forms of stress as cold, burns, hemorrhage, and painful nerve stimulation, etc., all cause a depletion of adrenal cholesterol and ascorbic acid, raises the question as to what common denominator is possessed by such stimuli. For, as we have seen, these alterations in adrenal composition depend on a preliminary activation of the anterior pituitary, and it is difficult to believe that the response of this organ is entirely nonspecific.

Two mechanisms may be considered as possible in so far as the liberation of adrenotrophic hormone is concerned. (1) Changes in the composition of the blood traversing the gland which act as an excitatory agent to the secretory cells. These changes may either be in the concentration in the blood of certain metabolites which follow the alterations in cellular activity or in the blood level of certain hormones. So far as the first is concerned there are a large number of possibilities none of which, however, appear at the moment to be acceptable as a common denominator in the conditions studied. The level of cortical hormone does appear to be of importance. Sayers and Sayers (2) have shown and we have confirmed that increasing the blood level by pretreatment of rats with the corticosterones prevents the usual fall in adrenal ascorbic acid and cholesterol of rats exposed to cold or subjected to unilateral adrenalectomy. It may, therefore, be surmised that exposure to a variety of stresses increases the tissue utilization of cortical hormones, lowering their level in the blood which in turn brings about activation of the

anterior lobe (2) Nervous control The question of a direct nervous control of anterior lobe secretion is a debatable one at the moment, but in so far as the types of stress outlined above are concerned there is very definitely one type of nervous activity associated with them all *This is an excitation of the autonomic nervous system and the release of its specific hormone, epinephrine* It was, therefore, of interest to determine the effects of epinephrine

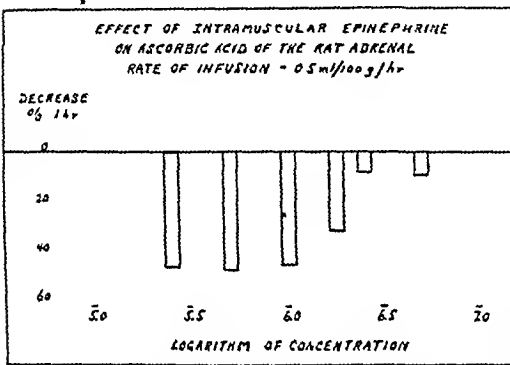


Fig 10 Effect of Intramuscular Epinephrine on the ascorbic acid of the rat adrenal Rate of infusion — 0.5 ml/100g/hr

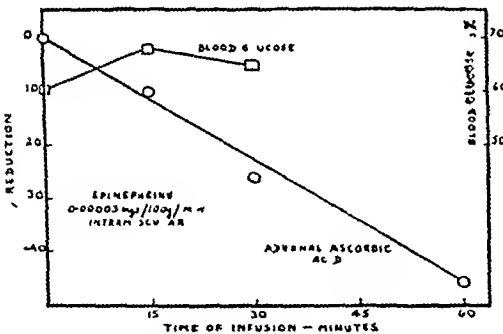


Fig 11 The effect of slow intramuscular infusion of epinephrine (1-1,000,000) on the blood glucose and adrenal ascorbic acid of the rat

in physiological amounts on the adrenal ascorbic acid and cholesterol of normal and hypophysectomized rats since all the conditions in which a fall in these substances occurred probably involved the discharge of this hormone

The results (figures 10 and 11) show that epinephrine injected either subcutaneously, intravenously or intramuscularly causes a fall in adrenal ascorbic acid and cholesterol to a similar degree and with similar time relationships to that found after the injection of ACTH It is, however, ineffective in hypophysectomized animals indicating that its action is exerted upon the anterior lobe

itself and not directly upon the cortical cells Vogt (17) has also found that epinephrine increases some 5-10 fold the content of cortical hormone in the plasma of the adrenal vein of dogs

Some additional points concerning this effect of epinephrine need to be considered The absence of any response in hypophysectomized rats is not due, as Vogt (18) has suggested, to the irresponsiveness of the gland as a consequence of the atrophy that normally follows the withdrawal of the trophic hormone This is shown by experiments in which immediately after hypophysectomy the animals were injected either with a crude extract of beef anterior lobes, purified adrenotrophic hormone or implanted each day with a rat anterior lobe (figure

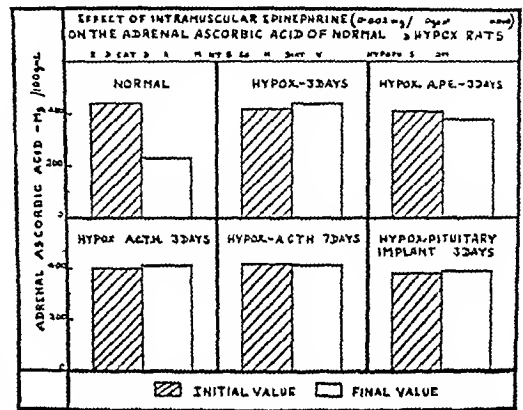


Fig 12 The effect of epinephrine (0.002 mg per 100 gs body weight per hour) on the adrenal ascorbic acid of (a) normal (b) hypophysectomized (c) hypophysectomized rats given the treatment indicated in the figure

12) Such procedures not only insure the maintenance of normal gland size and architecture but in some experiments produced glands larger than normal Nevertheless they still failed to respond to the administration of epinephrine

It is not yet known how epinephrine activates the anterior lobe It may stimulate cells normally receiving adrenergic fibres or since the presence of such nervous pathways to the anterior lobe is extremely uncertain, it may act directly on the secretory cells themselves in a manner analogous to its effect in promoting glycogenolysis in skeletal muscle Another possibility is that the hormone produces its effects on the anterior lobe by constriction of the blood vessels supplying the gland

None of these possibilities can as yet be said to have adequate experimental backing I would, however, like to point out that the use of these changes in adrenal ascorbic acid and cholesterol as indicators of the activation of the adrenotrophic

secretion opens the way for a more direct approach to the problem of the nervous or humoral control of anterior lobe activity

It is perhaps natural, at first sight, to regard this effect of epinephrine on the anterior lobe as simply another type of non specific stress. However, in the case of epinephrine we are dealing with a substance whose point of action is rather accurately known and although the present experiments are not sufficient to decide the exact manner by which it induces the secretion of adrenotropic hormone it at least is now possible to devise experimental conditions which will more directly answer this question

Finally, I would like to point out that the adrenotropic secretion is not the only anterior lobe hormone that appears to be influenced by epinephrine. Rowson and his colleagues (19) have recently reported that the injection of this hormone into rats not only discharged iodine from the thyroid but also increased the height of the glandular cells, both an indication of the release of thyrotrophic hormone. In addition Soffer et al (20) found that epinephrine increased to a significant degree the blood level of thyrotrophic hormone of normal dogs and that this also occurred in thyroidectomized or adrenalectomized animals

Markee, Sawyer and Hollinshead (21) report that ovulation occurring in rabbits after coitus is mediated by humoral rather than nervous means and that the humoral agent appears to be epinephrine since the direct application of this substance to the anterior lobe is followed by ovulation in a significant number of experiments. Similar applications of acetyl choline were ineffective

#### CONCLUSIONS

The experiments carried out in various laboratories in recent years indicate

1 The adrenotropic hormone whether injected or released under appropriate conditions from the anterior pituitary specifically decreases the cholesterol and ascorbic acid content of the adrenal cortex

2 These changes are associated with an in-

creased rate of secretion of the adrenal cortical hormones and may be used as indicators of such an increase

3 It is probable that the adrenal cholesterol is a direct precursor of the adrenal cortical steroids. It is not yet known whether the adrenal ascorbic acid is also directly concerned with the formation and release of these hormones or whether the observed changes represent its participation in metabolic transformations associated with the increased secretion from the gland. These experiments, however, do associate a vitamin with the secretory processes of an endocrine gland and point to a hitherto unsuspected role of the former in the organ from which it was first isolated

4 All circumstances known to be associated with an increased adrenal cortical secretion are also accompanied by a decline in these adrenal constituents but are without any such effect in the absence of the hypophysis

5 The stimulation of the elements of the autonomic nervous system with concomitant release of epinephrine that occurs under a variety of conditions appears to be a major factor in the activation of the adrenotropic secretion from the anterior lobe. The manner by which epinephrine produces this activation is not known. A further regulatory factor is the blood level of cortical hormones

6 The use of these changes in the chemical composition of the adrenal for the assay of adrenotropic hormone has already been reported. Their potential value for the determination of the mechanism of secretion of adrenotropic hormone by the anterior pituitary has been indicated

The experiments carried out in the Department of Physiological Chemistry have been conducted in collaboration with Dr and Mrs Sayers, Dr G Pinchot, Dr J Tepperman, Miss E G Fry, Dr H Gershberg and Dr Jine Oesterling. I am indebted to my colleagues for the use of certain hitherto unpublished experiments that are included in this paper. These studies have been assisted by grants from the Fluid Research Fund, School of Medicine, Yale University

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## THE PRESENT STATUS OF PTEROYLGLUTAMIC ACID AND OF OTHER HEMATOPOIETIC AGENTS

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About a year and a half ago interest in substances with antianemic activity became greatly heightened. This situation reflected the fact that the newly synthesized vitamin, pteroylglutamic acid (PGA), rather unexpectedly produced a striking hematopoietic effect in those types of anemia of man that are characterized by the appearance in the bone marrow and blood of abnormal macrocytic types of cells.

Since the demonstration by Minot and Murphy (1) in 1926 of the remarkable effect of liver in patients with pernicious anemia in relapse, many investigations have been directed toward the isolation of the substance or substances responsible for the hematopoietic effect. Isolation has not been accomplished, a situation that can be accounted for largely by the great difficulties attendant upon assay in suitable human patients with pernicious anemia in relapse. Despite these difficulties, considerable progress has been made in the purification of the liver factor, as indicated by the fact that many commercial extracts are available for parenteral use, in some of these an average daily dose of the factor is supplied by less than 10 mg of total solids. This dose may be contrasted with the daily oral dose of 300 to 500 grams of liver that Minot and Murphy found necessary. The available evidence suggests, however, that such liver extracts are still grossly impure.

As knowledge of a group of substances, variously termed norite eluate factor, *L. casei* factor, folic acid, vitamin B<sub>12</sub>, vitamin M, and otherwise, began to accumulate, it appeared increasingly likely that these substances play a very fundamental role in cellular metabolism, especially that concerned with hematopoiesis (2, 3, 4). However, its chemical and physical properties differ markedly from those

of active material in refined liver extracts, and animal and microbiologic assays of the latter disclosed only very small amounts of *L. casei* factor (5, 6). That pteroylglutamic acid could not be the erythrocyte-maturing factor of liver extracts is indicated by the fact that highly potent extracts do not give chemical tests characteristic of pteroylglutamic acid. Further, the *L. casei* factor is found widely distributed in the vegetable kingdom, while only materials derived from animal sources, such as liver, kidney and stomach, are efficacious in pernicious anemia, unless the materials tested are administered simultaneously with the gastric juice of normal individuals. Finally, the hematopoietic potency of the antipernicious anemia factor of refined liver extract is certainly greater, in terms of weight, than is that of pteroylglutamic acid. Accordingly, in this article, the term "antipernicious anemia factor" will refer to the hematopoietic substance found in refined liver extracts that appears to be chemically distinct from pteroylglutamic acid. Also, in order to avoid monotonous repetition, the term "folic acid" will be used synonymously with pteroylglutamic acid.

It is scarcely necessary to review the classic studies of Castle and his associates (7), through which it was shown that many natural materials contain a heat stable, extrinsic factor, that exerts an hematopoietic effect in pernicious anemia only when administered with a heat labile, intrinsic factor found in normal gastric juice. Neither this factor nor hydrochloric acid can be found in the gastric secretions of patients with pernicious anemia, and Addisonian pernicious anemia is believed to result from the gastric defect and the resultant failure in the utilization of certain substances of the diet that are essential to the formation of mature erythrocytes.

Although only meager information has been available concerning the properties of extrinsic factor, it is definitely not identical with any of the previously identified members of the vitamin B

\*Those studies carried out at Western Reserve University, reported herein, were supported by grants in aid from the United States Public Health Service and from the Lederle Laboratories.

complex (8). Since folic acid is less stable, at least in the forms known, and appears to be distributed in natural materials in a significantly different manner from that of extrinsic factor, there seemed little reason to postulate a relationship between folic acid and the extrinsic factor. Nevertheless, tests of crude concentrates of the *L. casei* factor, prepared from grass or spinach, were carried out by Moore, Welch and Wright in 1943 (9). A marked hemopoietic effect was obtained in one patient with pernicious anemia in relapse. In several other patients, however, disappointing results were obtained, presumably due to the administration of concentrates supplying amounts of folic acid adequate only for very susceptible patients. It was tentatively concluded that the one positive response obtained probably was due to a substance other than folic acid, and further study was prevented by the pressure of war research.

Castle and his associates (8) also tested, in two patients with pernicious anemia in relapse, the possible extrinsic factor activity of a naturally occurring derivative of pteroylglutamic acid, namely, fermentation folic acid, or pteroyldi-glutamylglutamic acid. Daily oral doses of 2.3 and 3.6 mg, respectively, were employed, but no effect was evidenced. Subsequently, this compound was found by Goldsmith (10) to have some activity in a patient with macrocytic anemia. Spies and associates (11, 12) noted activity in pernicious anemia; a pernicious anemia patient studied collaboratively by Castle and our group was shown to respond to the material and to excrete free *L. casei* factor in the urine, and Suárez, in collaboration with our group (13), demonstrated its high activity in sprue, a finding now adequately confirmed by others. It is possible that the first patients studied by Castle were both relatively insensitive to compounds of this type, or that both patients were unable to release pteroylglutamic acid from the complex. Since impure solutions of the fermentation factor are unpredictably unstable, it is also possible that the material supplied to Castle had decomposed prior to use.

Since it did not seem possible for folic acid to be either the extrinsic factor or the antipernicious anemia factor, it was somewhat surprising to many students of the problem when synthetic folic acid was reported by Spies, Vilter, Koch and Caldwell (14) to exert marked hematopoietic effects in certain macrocytic anemias, whether given parenterally or by mouth, without the participation of gastric juice. However, early confirmation of this finding was afforded by Moore, Bierbaum, Welch and Wright (9), who studied two cases of Addisonian pernicious anemia, one case of pernicious anemia of pregnancy and one case of sprue, with striking hematologic responses in each case.

Perhaps most logical, on the basis of the then

existing knowledge, was the finding that folic acid exerts a very beneficial effect in sprue. The work of Day and his associates (15) and of Doan and his group (16) had indicated that material with microbiologic activity for *L. casei* or *S. faecalis* is effective in monkeys deficient in vitamin M. In this condition the clinical picture and the changes in the blood very closely resemble those of sprue. Darby and Jones (17) probably were the first to test the activity of synthetic pteroylglutamic acid in sprue and their findings were confirmed by that of Moore and his associates (9), and by those of Spies and his group (18).

Darby and Jones (17) have suggested quite appropriately that vitamin M deficiency in the monkey may be considered to be the experimental analogue of sprue in man. Nevertheless, the two conditions differ fundamentally, since refined liver extracts have no apparent influence on vitamin M deficiency in the monkey, while in human sprue such extracts of liver have proved to be effective. The basis of this species difference in the response to the two substances is at present unknown.

The unexplained relationship of pteroylglutamic acid to the non-folic acid antipernicious anemia factor of liver has led to much speculation. Until recently it has not seemed reasonable to assume that two apparently chemically unrelated substances produce essentially identical hematologic responses through independent mechanisms. Accordingly, a common assumption has been that the function of the one substance is in some manner concerned with that of the other.

However, that pteroylglutamic acid functions as a precursor of the antipernicious anemia factor is most unlikely, because of the lack of chemical similarity between the two substances. For reasons already given, and for reasons to be given later, it is clear that pteroylglutamic acid is not related to extrinsic factor and it is obvious that the hematopoietic function of folic acid is not to stimulate the formation of intrinsic factor, since that substance, in contrast to pteroylglutamic acid, is quite inactive by itself. That the antipernicious anemia factor functions critically in the synthesis of pteroylglutamic acid is most unlikely, because several patients have been found in whom pteroylglutamic acid failed to produce a good response, although the subsequent administration of refined liver extracts produced an excellent hematopoietic effect (19, 20). Also refined liver extracts, in the majority of animal species, do not supply material which can be used in lieu of folic acid.

It is more difficult to rule out the possibility that pteroylglutamic acid is in some manner concerned with the synthesis of the antipernicious anemia factor. Considerable circumstantial evidence against this seemingly plausible effect of the substance is available, however. First, it would be

necessary to reason, in considering those patients in whom folic acid failed to produce a good response and liver extract was efficacious, that the system in which pteroylglutamic acid normally functions was defective. Second, animals severely deficient in folic acid would be expected to respond to refined liver extracts as well as to pteroylglutamic acid. Third, patients dying with pernicious anemia in relapse are known not to have antipernicious anemia factor in the liver, thus, a patient dying while in remission induced by pteroylglutamic acid would be expected to have antipernicious anemia factor in the liver, if the vitamin is concerned with the formation of the liver factor. A recent test of the liver of such a patient by Dr. C. V. Moore (personal communication), in an unfortunately rather complicated case, indicates that the amount of antipernicious anemia factor present was immeasurably small. We shall return later to the possible manner of action of the antipernicious anemia factor.

Several facts suggest that pteroylglutamic acid probably plays a very fundamental and essential role in human metabolism. Among these are not only its hematopoietic effect in the macrocytic anemias, but also its presence in combined form in the majority of animal and human tissues. The fact that it functions as an essential metabolite in bacterial, protozoan, animal, and even insect species, makes it most unlikely that man is an exception. The factor is synthesized by bacteria commonly found among the intestinal flora of several species and it is not impossible that it may be synthesized to some degree by animal tissues (21), although conclusive evidence concerning this point has not been made available.

A particularly strong argument that pteroylglutamic acid functions as a vitamin in man is afforded, of course, by the response of patients with macrocytic anemia, since only a vitamin-deficiency would be expected to respond so rapidly to the small doses which have proved to be effective. However, the reason for the difference between the manifestations of pernicious anemia and those of sprue is not clear. Also, the reason for the development of a deficiency of folic acid in individuals with pernicious anemia is not yet clear. The diet of such individuals usually is not greatly different from that of normal individuals, at least during the period prior to the development of a full blown anemic state. This failure of the pernicious anemic subject to subsist on ordinary sources of supply of folic acid suggested the possibility that in this disease some of the naturally occurring derivatives of the vitamin are not utilized effectively. Thus, it might have appeared possible for the extrinsic factor to consist of those conjugated forms of folic acid found in various foodstuffs, and that these under normal circumstances are broken down to

the free vitamin under the influence of the gastric intrinsic factor.

Through the generosity of Dr. J. J. Piffner of Parke, Davis, who isolated pteroylhexaglutamylglutamic acid from yeast, this hypothesis has been disproved, it was found that gastric juice does not release the *L. casei* factor from its hexaglutamyl conjugate (19). Evidence that the conjugated form of folic acid found in yeast does not function as extrinsic factor also was afforded by the finding that the compound was ineffective in some patients with pernicious anemia in relapse, whether given with or without gastric juice. However, in these patients daily oral dosage with an equivalent amount of synthetic pteroylglutamic acid caused a definite reticulocyte response (22, 19).

In collaboration with Jukes and Stokstad of the Lederle Laboratories, evidence suggesting that the extrinsic factor does not supply any utilizable form of pteroylglutamic acid, also has been obtained in rats and in chicks. Vacuum dried beef muscle, a commonly employed source of extrinsic factor, not only supplied a very small amount of folic acid, but also supplied no other substance utilizable by rats or chicks in the prevention or cure of a deficiency of pteroylglutamic acid. Further evidence is afforded by the finding that concentrates of extrinsic factor, representing a several thousand-fold concentration of milk, prepared in our laboratory in collaboration with Cistle, contain no significant amount of the *L. casei* factor.

The hexaglutamyl conjugate of folic acid, given either by mouth or parenterally to various animal species or to normal human subjects, appears to produce physiologic effects essentially indistinguishable from those of synthetic pteroylglutamic acid. Thus, the compound prevents or cures folic acid deficiency in animals, while in normal human subjects the administration of the conjugate, either orally or parenterally (22, 23), leads to the prompt excretion of free *L. casei* factor in the urine. In patients with pernicious anemia, however, the utilization of this substance appears to be much less certain. At first, it appeared that pernicious anemic patients characteristically cannot utilize the conjugate, but more recent findings have shown that this is not the case.

Thus, both our group (19, 22) and that of Bethell (23) described patients with pernicious anemia in relapse who failed to utilize the hexaglutamyl conjugate of the vitamin, although subsequent treatment with equivalent amounts of pteroylglutamic acid produced an hematopoietic effect. Microbiologic studies of the urine showed that, in contrast to normal human subjects, these patients derived an insufficient amount of free pteroylglutamic acid from the conjugate for appreciable augmentation of the urinary elimination of the vitamin.

These data were similarly interpreted by each of the two groups, namely, that one of the metabolic defects of pernicious anemia may consist of an abnormality in the derivation of pteroylglutamic acid from such naturally occurring derivatives as the hexaglutamyl conjugate of yeast. Not only was such an hypothesis consistent with the data obtained, but also it appeared to explain how individuals with pernicious anemia could become deficient in folic acid on diets not greatly different from those of normal subjects.

Recent developments, however, have indicated that the situation is much more complicated. Several laboratories, including those of Bethell, Castle, and ourselves, have obtained, in patients with pernicious anemia in relapse, good hematopoietic responses using new lots of the hexaglutamyl conjugate supplied by Dr Pfiffner. Studies of the urinary excretion of the free vitamin showed that these patients, unlike those who failed to respond hematologically, excreted free pteroylglutamic acid obviously derived from the conjugate.

It might be hypothesized that the patients most recently treated with preparations containing the hexaglutamyl conjugate of the vitamin suffered from a different form of macrocytic anemia than those studied first both by Bethell and by ourselves, but there is no evidence in support of such a view. A more logical theory would suggest that the first lots of conjugated vitamin differed in some respect from subsequent materials. Dr Pfiffner assures us, however, that essentially all the folic acid contained in the various samples was in the form of pteroylhexaglutamylglutamic acid, and that from such concentrates crystalline hexaglutamyl conjugate can be prepared.

A possibility of difference between the effective and the ineffective lots lies in the fact that at least two substances occur in yeast which are capable of inhibiting, *in vitro*, certain of the enzyme systems which release the free vitamin from its polyglutamates (24, 25, 13). These enzymes, termed conjugases, occur in nearly all animal tissues, including those of man, and it might be supposed that such enzyme-inhibitors occurred in a higher concentration in the original concentrates than in those studied subsequently. With such an hypothesis it would be necessary to reason, of course, that normal subjects would be relatively insensitive to the inhibitors, or would more rapidly inactivate them than would pernicious anemic subjects.

In support of such an hypothesis, Swenseid and her associates (24, 25) have suggested that an inhibitory substance in yeast, which has been studied *in vitro*, also exerts an effect *in vivo*. Thus, the urinary elimination of pteroylglutamic acid, following the daily oral administration of inhibitor-free hexaglutamyl conjugate, in an amount equivalent to 4 mg. of free vitamin, was about 30 per

cent of the dose administered in the absence of the inhibitor, but only about 5 per cent when administered with a source of the inhibitor. Addition of 30 grams of Difco yeast extract to the same oral dose of hexaglutamyl conjugate reduced the urinary excretory level of free folic acid from about 30 per cent to only about 2 per cent of the theoretical amount.

Thus, substances exist which can interfere with the absorption of the conjugate or with the derivation of free folic acid from it. That the substances which act *in vitro* are responsible for the action *in vivo* has not been established, nor is it known that the ineffective utilization of the earlier lots of conjugate was due to these same substances. Also, it has not been shown that patients with pernicious anemia are significantly less able to inactivate such interfering substances than are normal individuals. It might be supposed that the function of gastric juice is specifically to destroy such inhibitors, thus enabling conjugated forms of folic acid to be utilized. This view, which has been suggested by Swenseid (26), has not yet been put to test in a pernicious anemic patient by administering enzymes able to destroy the inhibitor of conjugase. However, the effectiveness of the inhibitors in normal individuals would appear to weigh heavily against this theory.

The theory that failure to utilize conjugated folic acid is to be attributed to simultaneously ingested inhibitors of conjugases unfortunately leaves unexplained one pertinent observation previously reported by our group (19). Although injected hexaglutamyl conjugate served as a source of free folic acid for urinary excretion in normal human subjects, no such urinary elimination followed the administration of crystalline conjugate in one pernicious anemic patient in relapse, even though the material was given intramuscularly in a dose of 30 mg. A subsequent equivalent intramuscular injection of synthetic folic acid in the same patient caused an excretion of 37 per cent of the dose. Whereas the crystalline conjugate yielded no hematopoietic response in this patient, the equivalent dose of pteroylglutamic acid caused a prompt reticulocytosis. Since the response to free folic acid indicates that the patient was not insensitive to pteroylglutamic acid, these results can only be explained, on the basis of the theory of inhibitors, by supposing that in this patient the various conjugases of the body were in a state of fairly complete inhibition.

It is obvious that our knowledge of the physiologic availability of the conjugated forms of pteroylglutamic acid which occur in foods and tissues is far from complete. Much more work is needed, but the material is so difficult to isolate and thus so expensive, that further advance may have to await another approach.



The possibility that factors in liver extract of high antipernicious anemia activity would be concerned with restoring the ability of patients to utilize hexaglutamyl conjugate, when previously they have been found unable to do so, has not been overlooked, either by Bethell's group or by our own. Results obtained *in vitro* (22), although at first encouraging, have proved disappointing on further study.

Bethell and his co workers have reported (24, 25) that orally administered conjugate, high in inhibitor content, contributed no more folic acid to the urine of a patient in relapse, during the daily administration of 15 parenteral units of liver extract, than was the case prior to such dosage. A patient in remission induced by folic acid excreted the same amount of vitamin, during the administration of a crude form of the conjugate, whether liver extract was given or not. Patients in remission induced by liver extract, however, excreted more folic acid in the urine, when given a conjugate high in inhibitor content, than did patients in relapse who were given the same material.

By using a subject free of the antipernicious anemia factor, it should be possible to test the concept that a factor found in liver extract is involved in some way with the utilization of conjugated folic acid. To that end we studied a patient whose relapse was so profound as to suggest the possibility that storage of antianemic factors might have been reduced to a minimum. On admission in coma, this patient had an erythrocyte count of only 340,000 per cmm of blood, the hemoglobin was 1.4 grams per 100 cc and the mean corpuscular volume was 117.5 cubic microns (all measurements were made in triplicate). Transfusions of blood were given to save the patient's life, but the only antianemic therapy employed was synthetic pteroylglutamic acid, parenterally administered in amounts totaling 90 mg daily. An excellent hematopoietic response was obtained later, when the patient was out of danger, a fairly crude solution of hexaglutamyl conjugate was administered parenterally, once daily for two days. Despite the presumed absence of the antipernicious anemia factor from the body, these injections led to the prompt excretion in the urine of free *L. casci* factor in an amount equivalent to about 25 per cent of the injected conjugate. Unless it be postulated that the previous therapy with pteroylglutamic acid had led to the synthesis of antipernicious anemia factor, which is now believed to be unlikely, it seems evident that either the antipernicious anemia factor was not completely absent from the tissues of this patient or the factor is not essential to the utilization of pteroylhexaglutamylglutamic acid.

Considering all the evidence, it might be concluded tentatively that substances found in liver

extracts may affect *indirectly* the utilization of conjugated folic acid by pernicious anemic patients, in some presently unknown manner improving the functional activity of various cellular systems and thus influencing favorably the utilization of conjugated forms of the vitamin. Conceivably, this may involve a more efficient handling of naturally occurring inhibitors of conjugases, but it must be emphasized that relapses can develop in pernicious anemia without any apparent defect in the handling of pteroylhexaglutamylglutamic acid, and that patients exist, who, in relapse, are unable to utilize even the crystalline form of this material.

In sprue, on the other hand, results have been obtained which suggest that factors of liver extract may affect rapidly the breakdown of conjugated forms of folic acid, particularly the fermentation form. A typical case of sprue studied by us, in collaboration with Dr. Ramón Suárez of the School of Tropical Medicine in Puerto Rico (13), was given 14 daily intramuscular injections of 4.9 mg of pteroyldiglutamylglutamic acid supplied by the Lederle Laboratories. All manifestations of the disease were promptly improved and the hematologic response was excellent. Analyses indicated that the conjugate was broken down to free folic acid, since the average urinary excretion of the vitamin was equivalent to about 40 per cent of the material administered, a magnitude of excretion which compares favorably with that following the administration of comparable doses of synthetic pteroylglutamic acid. However, a remarkable change in this excretion occurred on the eleventh day, simultaneously with the initiation of the daily intramuscular administration of 1 cc of an extract of liver containing 15 units of antipernicious anemia activity and less than 0.001 mg of microbiologically determinable folic acid. On each of the first two days of therapy with the liver extract, the urinary elimination of folic acid rose from the previous level of about 40 per cent to about 250 per cent of the daily intake in the form of the conjugate. On the third day of combined therapy the excretion had fallen to 25 per cent of the administered conjugate. It is difficult to explain these findings without attributing to the liver extract some influence on the metabolism of stored forms of pteroylglutamic acid.

In pernicious anemia, however, such an effect on the urinary elimination of folic acid during the administration of pteroyldiglutamylglutamic acid was not seen in a case studied by us in collaboration with Dr. W. B. Castle.

In another patient with sprue, a concentrate of yeast containing pteroylhexaglutamylglutamic acid was given. The daily oral dose of this material, which was reported to be free from conjugase inhibitors, was equivalent to 8.4 mg of free folic

acid With this material also, a good hematologic and clinical response was obtained However, until the fifth or sixth day the excretion of folic acid was not appreciably augmented from the pretreatment level of about one microgram daily On the seventh day, when reticulocytes already composed about 24 per cent of the circulating erythrocytes, the urinary excretion of the free vitamin was only 54 micrograms In this case, liver extract was given simultaneously, after an initial ten day period of therapy with the conjugate alone Whereas the urinary excretion of folic acid prior to and on the first day of therapy with liver extract corresponded to only about 4 per cent of the orally administered conjugate, this was increased to an average of 14 per cent daily on the following three days This increase is, of course, much less striking than that which occurred during therapy with the dglutamyl conjugate and cannot safely be attributed to the effect of the liver extract Further studies will be necessary in order to prove whether in patients with sprue, in contrast to those with pernicious anemia, liver factors rapidly influence the utilization of conjugated forms of folic acid

Many of the problems discussed here, together with a number of others, might be attacked more effectively if a compound were available with which the function of pteroylglutamic acid could be blocked effectively Chemical analogs or metabolite antagonists have been developed for a large number of essential metabolites, including all the known members of the vitamin B complex, a field reviewed by this author (27) and more recently by Roblin (28) Martin and his associates reported recently (29) the synthesis of a compound that interferes with the utilization of folic acid by *S. faecalis* This compound, referred to as d(-)methyl-folic acid, was prepared by a method analogous to that used for the synthesis of pteroylglutamic acid (30), except that p-aminobenzoyl-d(-)-glutamic acid was used, and 2,3 dibromobutyraldehyde was employed in place of the corresponding three-carbon compound

For several months we have had the privilege of studying limited amounts of an effective antagonist of pteroylglutamic acid, prepared by Dr M E Hultquist and Dr J M Smith, Jr, of the Calco Chemical Company and generously supplied to us by the Lederle Laboratories Jukes, Stokstad, Franklin and Belt have carried on extensive studies of this antagonist, used in the form of the crude product of the reaction between 2,4,5-triamino-6-hydroxy-pyrimidine, p-aminobenzoyl-1(+)-glutamic acid and 2,3 dibromobutyraldehyde

These workers have found (31) that the antagonist reversibly inhibited the growth of *Streptococcus faecalis* R and *Lactobacillus casei* When fed to rats in the form of a purified diet containing

succinylsulfathiazole, the evidences of deficiency of folic acid were more marked than those observed in the absence of the antagonist Signs of the deficiency included very ruffled fur, inhibition of growth, characteristic chromodacryorrhea, depression of the leucocyte, and particularly of the granulocyte count, a depression of the hemoglobin level, and the appearance of oral lesions not previously observed in folic acid deficient rats Not only was it possible to prevent these changes by the inclusion of pteroylglutamic acid in the diet, but also, when the deficiency syndrome was established, recovery was initiated by the addition of the vitamin to the ration

In mice (32), the purified diet containing succinylsulfathiazole produced no evidence of deficiency in six weeks, unless the antagonist was also included in the diet, at that time a majority of the antagonist fed mice were dead In chicks also the antagonist proved very effective

In our laboratory, we have been interested particularly in the use of this antagonist for the production of pteroylglutamic acid-deficiency in swine Our attention was attracted to this species because pigs have previously been used for the production of anemia that resembles human macrocytic anemias and that apparently responds to therapy with liver extracts Thus, Miller and Rhoads (33) described in 1935 the production of a dietary anemia in pigs and its treatment with liver extract, and Cartwright, Wintrobe and Humphreys (34) reported about a year ago the production of a severe growth depression and anemia in a pig fed a purified diet containing succinylsulfathiazole The growth depression and anemia responded strikingly to therapy with refined liver extract Although we (35) have not been able to reproduce the deficiency described by Wintrobe and his associates, biotin was present in the purified diet of our pigs, a factor which was omitted from the diet used by the Utah group, it is possible that this difference may be significant

It has been encouraging to find, however, that as a result of a single modification of the purified diet of one pig, namely, the inclusion of the crude antagonist of pteroylglutamic acid previously mentioned, a depression of appetite and growth gradually developed, together with severe anemia Profuse diarrhea was noted, the animal became listless and evidenced an unwillingness to stand, although no signs of neuromuscular degenerative changes were found The condition progressed until the continued survival of the animal became doubtful

At this time the purified casein (Labco) of the diet was withdrawn and was replaced by crude sodium caseinate in equivalent amount (20 per cent) Because of the low food intake the pig

also was given, by daily gastric intubation, for ten days, an alcohol extract of crude casein in an amount equivalent to about 100 grams of casein, together with from 80 to 150 cc of fresh neutralized human gastric juice. Crude casein has been shown by Castle and his associates (8) to be a source of extrinsic factor, while alcohol extracted casein appeared to be devoid of the material. Our extract of casein was prepared by exhaustive extraction of crude casein with hot 95 per cent ethanol and was shown to be a source of extrinsic factor by human assay. None of the materials administered contained appreciable amounts of microbiologically determinable pteroylglutamic acid. After ten days of treatment with the extract of casein and gastric juice, and a total of fourteen days on the diet containing sodium caseinate, the pig was returned to the original purified diet.

As a result of the supplementation, improvement in appetite and vigor were rapid and unmistakable. The stools, previously diarrheic, assumed a semi solid consistency, within less than two weeks the animal was normal with respect to appetite, alertness and strength. On the eleventh day after supplementation was begun, the reticulocyte count began to increase, three days later the level was 9 per cent and a peak of 11 per cent was attained after an additional five days. It is to be noted that the improvement in appetite, growth and hematopoiesis, initiated by the supplementation, has continued unabated to the present date, approximately ten weeks from the cessation of therapy.

It cannot now be stated that the response of the pig to the administration of a crude source of extrinsic factor, together with normal human gastric juice, was due to the combined effect of the two materials. A preliminary trial of the casein extract alone was prevented by the severity of the syndrome that developed. It is unlikely that gastric juice would have been efficacious by itself, since the studies of Castle and his associates have shown adequately that intrinsic factor alone produces no significant hematopoietic effect in human patients with pernicious anemia in relapse. Whether the pig had developed a deficiency of intrinsic factor cannot be stated, although a gastric analysis about three weeks prior to the institution of therapy indicated a high total acidity with absence of free hydrochloric acid. Studies designed to answer some of these questions are now in progress.

The many possible applications of the folic acid antagonist to the study of the function of the vitamin and even for therapeutic use are most intriguing and some of these are now being investigated. The utilization of the antagonist of folic acid for the production of an animal in which the study of the extrinsic factor and possibly the

antipernicious anemia factor can be advanced appears particularly promising and a program of concentration of extrinsic factor is under way.

Preliminary information of great interest concerning the results of studies now in progress in the laboratories of Daft (21) and of Elvehjem (36) has just become available. Daft has found that rats fed a diet containing only 4 per cent of casein develop anemia and leucopenia and that the leucopenia responds to refined liver extract. The Wisconsin group has found that a purified diet deficient in niacin permits the development in the dog of a deficiency that eventually ceases to respond to niacin. Signs of the deficiency, which include diarrhea and anemia, do not respond to folic acid. Refined liver extracts are very effective when the diet is high in casein or when supplements of pteroylglutamic acid are given, but the liver extracts apparently produce little or no response in the absence of pteroylglutamic acid.

It is clear that in several laboratories work is in progress which promises soon to solve some of the mysteries which have complicated the biochemistry of the synthesis of new cells, particularly of those found in the blood. At present, however, the information available does not permit us to do more than speculate concerning the relationship of the several factors involved.

To leave the subject at this point is most unsatisfactory, but the data available are not yet adequate for a clear picture to be drawn of the functional relation between pteroylglutamic acid and the antipernicious anemia factor. Although it is dangerous indeed to speculate at this time, it is tempting to suggest a new theory which appears to reconcile some, but not all, of the apparently conflicting data.

For the formation of erythrocytes and leucocytes, and doubtless of other types of cells, many compounds must be formed. For the synthesis of some of these, let us suppose that the antipernicious factor is utilized catalytically, presumably in the form of one or more enzymes. But, let us suppose also that in man another pathway of synthesis of some of these compounds, and probably of other compounds as well, is catalyzed by pteroylglutamic acid. Thus, the human subject might be supposed to derive material suitable for the formation of new erythrocytes by virtue of either type of catalysis, because of the overlapping in the synthetic accomplishments of the two factors. Very likely, however, neither factor can be wholly dispensed with and the state of pernicious anemia would reflect a deficiency of both substances. That pteroylglutamic acid is not able entirely to replace the factors found in refined liver extracts is shown by the neurologic relapse observed in some patients whose hematologic maintenance on pteroylglutamic acid has been

excellent (37, 38). Apparently factors supplied by liver extracts are involved in the formation of substances that are essential to the integrity of the nervous system. Whether the factors of refined liver extract can replace completely the folic acid requirement of man cannot be decided definitely at this time, but clinical evidence suggests that they cannot. It is obvious that the antagonists of folic acid may prove helpful in obtaining an answer to this question.

The relative importance of the two anti-anemic factors may vary in different animal species. Thus, the results in the dog, obtained in Elvehjem's laboratory (36), suggest the possibility that a factor found in refined liver extract cannot replace the need for folic acid. In most animals studied, the requirement for pteroylglutamic acid cannot be obviated by administering refined liver extracts, probably because there is no deficiency of the factors supplied by the liver fraction and in these species the catalytic effects of folic acid are indispensable. However, in man, and possibly in the pig, the available evidence suggests that a majority of the materials required for the synthesis of red cells may be formed through the catalytic effects of either pteroylglutamic acid or factors of refined liver extract.

That one of the compounds synthesized for blood cell formation may be a derivative of thymine is suggested by the fact that Stokes (39) has found in the presence of this compound

certain bacteria no longer require folic acid, and Frommeyer and Spies (40) have demonstrated the partial effectiveness of massive doses of thymine in nutritional macrocytic anemia, pernicious anemia and sprue. The evidence strongly indicates, however, that other compounds are important, since the effects obtained with thymine in man are less satisfactory than with pteroylglutamic acid or liver extracts, and because thymine will not relieve the manifestations of folic acid deficiency in animals.

The hypothesis presented in this paper appears to fit much of our present knowledge, but there is as yet no definite evidence in favor of it, or of any other explanation of the relation between the antipernicious anemia factor and pteroylglutamic acid. It may be pointed out, however, that the striking response of the pig, almost certainly unable effectively to utilize pteroylglutamic acid, to the administration of a folic acid-free concentrate containing extrinsic factor, given with normal gastric juice, offers evidence that is difficult to interpret in any other manner.

In conclusion, it is firmly stated that these working hypotheses and conjectures are the figment of the author's imagination. His valued colleagues, particularly Dr. Robert W. Heinle, without whom many of the studies reported here would have been impossible, should not be held to account for the speculations with which this article is concluded.

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## BACTERIAL TOXINS<sup>1</sup>

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Diphtheria, tetanus and botulism are well known diseases of bacterial origin, the symptoms of which may be reproduced in experimental animals by injection of sterile culture filtrates containing diphtheria, tetanus and botulinus toxins, respectively. The nature and mode of action of these three powerful poisons has been a problem of outstanding interest since their discovery more than 50 years ago. In this review, we propose to discuss some of the evidence concerning the nature of these bacterial toxins, from the standpoint of (1) their chemical properties, (2) the anatomical and pharmacological changes they bring about in susceptible animals, (3) the biochemical lesions they produce in the intoxicated host and finally, (4) their role in the metabolism of the microorganisms themselves.

*Isolation and Chemical Properties of the Bacterial Toxins* All three bacterial toxins have now been isolated as highly purified heat labile proteins. Diphtheria toxin was isolated and characterized some years ago by Eaton (1) and by ourselves (2). More recently, Pillemer and Toll (3) have used improved methods of alcohol fractionation at controlled pH and ionic strength to isolate diphtheria toxoid (i.e. formalin treated toxin). Within the past year, crystallization of both tetanus and botulinus toxins was reported. Tetanus toxin was isolated in highly purified crystalline state by Pillemer et al (4). Two groups working independently at Camp Detrick, Lamanna and his associates (5) and Abrams, Kageles and Hottel (6) crystallized and

characterized botulinus toxin, Type A. In every instance, isolation was facilitated by the use of media of chemically defined or simple composition for cultivation of the organisms.

In Table 1 we have summarized some of the chemical and physical properties of diphtheria and botulinus, Type A, toxins. Comparable data for crystalline human serum albumin are included for comparison. Tetanus toxin is not included in Table 1, because analytical data have not yet become available for the crystalline protein. It is quite clear that the chemical differences are quantitative and provide no obvious clue as to why one protein is toxic and another is not. Nor have studies on toxoid formation shed much light on the problem. The amino acid composition of botulinus toxin as determined by the Camp Detrick workers has accounted for more than 73% of the protein molecule, yet no characteristic toxic grouping has been revealed.

Up to the present, all methods which denature or in any way alter the three proteins, bring about a simultaneous loss of toxicity. Both tetanus and diphtheria toxins are rapidly destroyed by proteolytic enzymes. Botulinus toxin, on the other hand, is relatively resistant to the action of pepsin and trypsin and is the only one of the three toxins which is effective when administered by mouth.

*Morphological and Physiological Changes in Intoxicated Animals* The toxicity of the three toxic proteins for the guinea pig and for the mouse is summarized in Table 2. Their extreme toxicity is even more startling, perhaps, when one considers that one milligram of tetanus or botulinus toxin is sufficient to kill more than 1000 tons of guinea pig!

<sup>1</sup> Supported by a grant from The Commonwealth Fund.

The molecular weight of botulinus toxin is 900,000 (9) from which it may be readily calculated that only 20,000,000 molecules are necessary to kill a mouse. It is clear that each of the three toxins is active at an effective concentration of only one molecule per cell and even at this concentration only a small fraction of the animal tissue can be

TABLE 1  
Properties of bacterial exotoxins

	DIPH THERIA TOXIN*	BOTULI NUS TOXIN TYPE A†	HORSE SERUM ALBU MIN‡
Nitrogen (per cent)	10.0	14.1	15.9
Sulfur	0.75	+	1.03
Phosphorous	<0.05	<0.045	negative
Amino nitrogen	0.98	—	—
Cystine	—	0.5	5.7
Methionine	—	0.8	—
Tyrosine	9.5	9.5	4.8
Tryptophane	1.4	+	0.53
Arginine	3.8	3.2	4.9
Histidine	2.4	1.0	3.4
Lysine	5.3	7.9	13.2
Iso electric point	4.1	5.6	4.9
Sedimentation constant	4.0 S	17.3 S	4.46 S
Diffusion Constant $\times 10^7$	0.0	2.14	0.1
Fractional Coefficient f/f <sub>0</sub>	1.22	1.76	1.27
Molecular weight	72,000	900,000	70,000

\* Pappenheimer (2)

† Compiled from data of Abrams et al. (6), Lawanna et al. (5), Buehler et al. (7), Kegeles (8), Putnam et al. (9)

‡ Brand (10)

TABLE 2  
Toxicity of purified bacterial toxin\*

ANIMAL	TOXICITY (MLD PER KILO ANIMAL PER MG TOXIN)		
	Diphtheria toxin	Tetanus toxin	Botulinus toxin
Guinea pig	3500	1,200,000	1,200,000
Mouse	3.5	200,000	300,000

\* For the sake of comparison the toxicity has been expressed as minimal lethal dose per kilo of animal per mg of toxin. The toxicity of tetanus and botulinus toxin for guinea pig was calculated from the ratio of their toxicity for the guinea pig to that for the mouse as given by von Lindeheim (11) and Meyer (12) respectively. Similarly the toxicity of diphtheria toxin for the mouse was calculated from the data of Jungeblut (13).

directly effected. How may we account for their extraordinary potency? By what means do they cause injury to the cells of susceptible animals?

The pharmacological action of the bacterial toxins is specific for each toxin. The action of tetanus toxin in particular, has been the subject of much study. Animals which succumb to tetanus intoxication show no gross or microscopic lesions. The classical work of Marie and Morax (14) and of Meyer and Ransom (15) indicated that tetanus

toxin is taken up by the motor nerve endings and reaches the anterior horn cells of the central nervous system by way of the axis cylinders. The anterior horn cells are then stimulated to produce muscular contraction. A controversy has grown up in recent years concerning the manner in which the toxin reaches the anterior horn cells and also over the question of whether involvement of the central nervous system is essential for the production of local tetanus (16, 17). Any adequate and critical discussion of the vast amount of work in this field would constitute a review in itself.

Botulinus toxin is also a neurotoxin. According to Bishop and Bronfenbrenner (18) it acts specifically on the myoneural junctions and has a "curare-like" action. Death is due to respiratory paralysis.

In contrast to tetanus and botulinus toxins, diphtheria toxin is quite non specific in its action. Diphtheria toxin may cause injury to almost any of the tissues of susceptible animals including skin, muscle, nerve, lung, liver, adrenals, etc. When a minimum lethal dose (MLD) of toxin is injected into a guinea pig, death occurs in 4-5 days and on autopsy, gross hemorrhagic edematous or necrotic lesions may be found in all these tissues. The wide distribution of the lesions may explain in part why diphtheria toxin is less toxic than either of the aforementioned neurotoxins.

Although the three toxins are quite distinct in their pharmacological properties, their toxic actions show certain features in common which serve to distinguish them from other toxins of animal, plant and bacterial origin. Tetanus, botulinus and diphtheria toxins are all capable of causing injury to tissues in doses containing a relatively small number of molecules. When administered in 1-2 MLD doses, each of the three toxins show a prolonged latent period (18-72 hours or even longer) during which no symptoms or lesions can be demonstrated. Yet it is certain that some irreversible damage is caused within a few minutes or seconds after the toxin has been injected. Thus even 1000 units of diphtheria antitoxin injected 15 minutes after 1/50 MLD of toxin has been injected in the skin at the same site fails to prevent a positive reaction from appearing 24-48 hours later. Yet only 0.001 unit of antitoxin mixed with this small amount of toxin before injection suffices to neutralize its toxic action. The characteristic latent period and the extraordinary potency of these toxic proteins suggest that they do not act by direct inhibition of enzymes nor as enzymes themselves but rather perhaps, by interfering with the synthesis of some essential enzyme. Toxic symptoms, then, would not be manifested until the excess of essential enzyme has become depleted. This is not to say that none of the bacterial toxins is an enzyme or interacts directly with enzymes. It will be recalled that the lethal or  $\alpha$ -toxin produced by another

bacterial species, *Cl welchii*, is a lecithinase which hydrolyses lecithin to phosphorylcholine and a diglyceride (Macfarlane and Knight, 19) The MLD of the purest preparations of lecithinase, however, is some 10,000 times greater than the toxins we have been considering and its action is immediate rather than delayed

**Biochemical Lesions in Intoxicated Animals**  
The swollen red adrenal glands, so characteristic of diphtheria intoxication in the guinea pig have lead many workers to try to demonstrate relationships between Vitamin C, adrenalin and the cortical hormones with the toxin No clear cut interaction or relationship between these substances and diphtheria toxin has been found

Peters and Cunningham (20) have carefully tested the effect of diphtheria toxin on a number of enzyme systems found in normal heart muscle No significant effect could be detected upon any of the systems which they studied Disturbances in carbohydrate metabolism in animals due to diphtheria toxin are well known however Recent metabolic studies on intoxicated animals have been reviewed by Holmes (21) It has been demonstrated that intoxicated animals develop a resistance to the action of insulin (22), a diminished capacity to synthesize carbohydrate (23) and to metabolize lactic acid (24) Such changes, however, are only evident after a period of at least 18-24 hours in animals receiving relatively small but lethal doses of toxin As Holmes (21) points out, similar biochemical changes can be produced in experimental animals by causing liver damage with non specific agents such as carbon tetrachloride and chloroform Thus, as in the case of the anatomical lesions, the observed changes are probably secondary to a primary and more fundamental injury

**Function of Diphtheria Toxin in the Bacterial Cell**  
An approach to the problem of finding out the nature of the primary damage caused by diphtheria toxin has recently suggested itself This method rests on the thesis that if the role which the toxin plays in the metabolism of the diphtheria bacillus itself can be determined then it may well be possible to predict the manner by which it causes injury to the cells of higher animals

Certain observations on toxin production have indicated that diphtheria toxin may in some way be concerned in oxidation mechanisms Firstly, toxin is produced only under strict aerobic conditions, i.e. by growing the organisms on a shallow layer of medium or by vigorous shaking of the culture with air (Langbeek, 25) Secondly, toxin is produced in high yield only when the iron concentration is reduced to a very low level (ca  $2 \times 10^{-6}\%$ ), below that optimal for growth and far below that present in normal tissues Finally, a porphyrin is found in culture filtrates only when the iron concentration is reduced Yields of porphyrin and

toxin parallel one another closely Recently, the inhibition of toxin and porphyrin production by iron has been reinvestigated quantitatively (26) The results show that for every 4 atoms of iron added to the medium on which the diphtheria bacillus is grown (over and above that optimal for toxin production), 4 molecules of porphyrin and 1 of toxin fail to appear in the culture supernatant All of the iron added over the range where toxin production is inhibited can be found within the cells Moreover, as the cellular iron content increases, a two-banded hemochromogen type of spectrum appears in cell suspensions treated with dilute alkali and sodium hydrosulfite These findings suggest the possibility that diphtheria toxin may be the protein moiety of an iron containing respiratory enzyme, as globin is the protein moiety of hemoglobin The following scheme has been outlined as a working hypothesis It is probable that diphtheria bacilli grown on media deficient in iron retain their capacity to synthesize porphyrin and protein moiety (toxin) Because sufficient iron is lacking to synthesize the complete enzyme, the porphyrin and toxin are excreted as waste products When excess iron is present they are retained by the cells as the complete enzyme Cells grown in media containing excess iron have an iron content of ca 0.85 mgs per gram bacterial nitrogen, or about 5 times the iron content of cells grown under conditions optimal for toxin production Furthermore, toxin is a highly specific protein, and according to our findings the amount which the cells fail to excrete is equivalent to the iron added It might be expected, therefore, that the proposed toxin containing enzyme would be the major respiratory pigment of the cell As will be discussed presently, the major pigment found in diphtherial cells of high iron content is spectroscopically related to cytochrome b

**Effect of Iron on Catalase Production** We have attempted to identify the unknown enzyme composed of iron, porphyrin and possibly diphtherial toxin by measuring the effect of iron on the production of various iron enzymes by the diphtheria bacillus Several years ago, Mueller (27) referred to unpublished experiments by Fox and Klotz demonstrating that catalase activity of the diphtheria bacillus was increased when grown on media containing an excess of iron The data shown in Table III confirm their findings The catalase content of organisms of the Toronto strain is proportional to the iron added and to their iron content over the range in question and inversely proportional to toxin production Crystalline catalase contains 30-60,000 units per gram and its iron content is 0.09% (28) From these figures and the data given in Table 3 it may be calculated that the increase in catalase iron is only 1-2 micrograms per gram of bacteria as compared with a total increase in cell-



ular iron of 70-80 micrograms per gram Catalase, therefore, is most unlikely to be the toxin containing enzyme

*Effect of Iron on Succinate Oxidation by Whole Organisms* Table 4 summarizes the results of several experiments on succinate oxidation by suspensions of diphtheria bacilli of varying iron content. Here again the enzyme activity is proportional to the iron added and the bacterial iron content over the range studied and is inversely proportional to extra-cellular toxin production.

The rate of oxidation of succinate may sometimes give an approximation of the overall activity of the cytochrome system. For estimation of the relative amounts of the individual cytochrome

TABLE 3  
*Effect of iron on catalase production*

IRON ADDED	FW #8 (TORONTO) STRAIN	
	Growth	Catalase
$\mu\text{g per 300 cc}$	$\text{mgs N}$	$\text{Kat f}$
0	162	185
50	215	400
100	228	610
200	240	840

TABLE 4  
*Effect of iron on succinate oxidation*

IRON ADDED	FW #8 (TORONTO) STRAIN	
	Toxin	$\text{QO}_2$
$\mu\text{g per 300 cc}$	$\text{Lf/cc}$	$\text{mm}^3 \text{ O}_2/\text{mg N/hr}$
0	70	20-30
20	62	35-50
50	48	43-66
70	40	72
100	25	110
200	0	106-120

components, however, it is necessary to extract them quantitatively from the cell. We have found the 9000 cycle sonic oscillator manufactured by the Submarine Signal Corporation of Boston suitable for this purpose. Heavy suspensions of diphtheria bacilli (ca. 5-10% dry weight) may be completely disrupted in 30 minutes. After centrifuging in a Swedish angle centrifuge the opalescent supernatant contains at least 90% of the activity of the whole organisms when tested against succinate.

Such extracts from high iron containing organisms are deep reddish brown in color. Organisms grown under conditions optimal for toxin production, on the other hand, yield pale straw-colored extracts. When examined spectroscopically following reduction with hydrosulfite the extracts from high iron cells show three bands with maxima at 428, 524, and 560 m, wavelengths characteristic of the b-component of the cytochrome system. The corresponding bands for cytochrome b in heart muscle

as given by Keilin and Hartree (29) lies at 432, 530 and 564 m and for cytochrome b<sub>L</sub> from yeast, in the visible region, at 530 and 556.3 m (Bach, Dixon, and Zervas, 31). Cytochrome b thus appears to be the major iron containing constituent of the diphtherial cell, in confirmation of data reported by Fujita and Kodama in 1934 (30). It is readily autoxidizable and its oxidation by molecular oxygen is not inhibited by 0.003 M cyanide. At least a portion of diphtherial cytochrome b appears to be firmly bound to large molecular components contained in the extracts since about 30% is completely sedimented from solution after 2 hours centrifugation at 18,000 r.p.m. It may be partially purified by this means.

The role of cytochrome b in mammalian tissue respiration is still uncertain. Keilin and Hartree (29), Ball et al. (32) and others are of the opinion

TABLE 5  
*Effect of KCN on  $\text{O}_2$  uptake by Toronto strain grown in excess iron*

ENZYME PREPARATION	SUBSTRATE	KCN	$\text{QO}_2$	INHIBITION
			$\text{mm}^3 \text{ O}_2/\text{mg N/hr}$	
		$\text{mols/liter}$		per cent
Whole organism	Succinate	0	85	0
		$2.5 \times 10^{-4}$	60.5	29
		$2.5 \times 10^{-3}$	54.5	36
Sonic extract super- natant from 45 min at 18,000 r.p.m.	Succinate	0	75	0
		$2.5 \times 10^{-4}$	59	20
		$2.5 \times 10^{-3}$	59.5	19.5
Same	Phenyl enedia mine	0	17	0
		$2.5 \times 10^{-3}$	0	100

that it is concerned in the oxidation of succinate where it may serve as a link between succinic dehydrogenase and the cytochrome c-cytochrome oxidase system. There is no evidence at present that heart muscle preparations containing cytochrome b can oxidize succinate in the absence of cytochrome c and cytochrome oxidase, unless some other catalyst such as methylene blue is added.

It seems almost certain that diphtherial cytochrome b is directly concerned in the oxidation of succinate. Studies with the diphtheria bacillus have shown that its succinoidase system differs in certain important respects from that of mammalian cells. The evidence for these conclusions may be summarized as follows:

1. Diphtherial cytochrome b is readily autoxidizable (probably more rapidly than cytochrome b from heart muscle) and its autooxidation is not inhibited by potassium cyanide.

2. Oxidation of succinate by intact diphtheria bacilli of high iron content is only 30-40% inhibited even in the presence of  $2.5 \times 10^{-3}$  M KCN. Oxidation by heart muscle preparations is completely inhibited by cyanide (Table 5).

3 Extracts from bacteria disrupted by sonic vibration, which have been centrifuged for 30 minutes at 18,000 r p m to remove the larger bacterial fragments are still inhibited 10-20% by KCN. If such extracts are allowed to stand for a few days, slight loss of activity occurs and the preparation becomes completely insensitive to cyanide. Such succinoxidase preparations are very stable and show no loss in activity even after storage for weeks in the cold.

4 The rate of oxidation of succinate by such crude extracts is roughly proportional to their cytochrome b content as estimated from the intensity of their absorption at 560 m $\mu$ , after reduction with sodium hydrosulfite.

5 Addition of succinate, under anaerobic conditions brings about the rapid reduction of cytochrome b in diphtherial extracts. As would be predicted from the relative oxidation potentials of the succinate-fumarate and cytochrome b systems ( $E_0 = -0.00$  and  $-0.04$  respectively at pH 7.0, Ball, 33), this reduction is not complete. If air is now admitted to the system, the intensity of the cytochrome b band at 560 m $\mu$  is diminished, indicating its reoxidation. The identical behavior is observed in the presence of KCN.

6 Cytochrome c is present in very low or even negligible concentration in extracts which bring about the rapid oxidation of succinate. Fujita and Kodama (30) reported the presence of a weak band at 550 m $\mu$ , corresponding to cytochrome c, in suspensions of diphtheria bacilli grown on blood agar. We have fractionated the extract from 3 gms of diphtheria bacilli according to the method of Stotz (34) for determination of cytochrome c in tissues. Even when concentrated to a volume of 2.5 cc, no cytochrome c could be detected using phenylenediamine and a cytochrome oxidase preparation from rabbit kidney cortex. Addition of 0.2 mgs cytochrome c to the test system increased its rate of oxygen uptake by 50%.

Finally, it may be added that for each mol of succinate oxidized by cytochrome b containing extracts, 0.5 mols of oxygen are consumed, suggesting that fumaric acid is the product formed. As with all succinoxidase preparations, malonate is a powerful inhibitor. Diphtherial extracts again differ from heart muscle enzymes, however, in that the naphthoquinone SN 5949 even at a concentration of 100 mgs./liter fails to inhibit the oxidation of succinate. Bill and his associates (32) have recently shown that oxidation of cytochrome b in heart muscle suc-

cinoxidase preparations is completely inhibited by this compound at a concentration of only 1 mg./liter. It has no effect on the oxidation of phenylenediamine by cytochrome c cytochrome oxidase.

Before concluding this discussion, it seems worthwhile to refer briefly to the cytochrome oxidase activity of the diphtheria bacillus. In addition to succinate, glucose, maltose, lactate and other substrates are rapidly oxidized by intact diphtheria bacilli of high iron content and oxygen uptake with these substrates is only partially inhibited by cyanide. Phenylenediamine and hydroquinone are not oxidized by the whole organisms, probably because the cell is impermeable to them. Fresh cell extracts, however, do oxidize hydroquinone and phenylenediamine, at a relatively slow rate, approximating that fraction of succinate oxidation inhibited by cyanide. Moreover, phenylenediamine oxidation is 100% inhibited by KCN. At present, we are unable to reconcile the oxidation of phenylenediamine with our failure to detect cytochrome c in diphtherial extracts. The enzyme concerned in phenylenediamine oxidation possesses many of the properties of cytochrome oxidase including cyanide sensitivity, extreme lability and association with the heavier cell fragments. The oxidation of phenylenediamine is only slightly accelerated by addition of cytochrome c (10-20%).

While it is our present opinion that diphtheria toxin is the protein moiety of cytochrome b, it should be clearly understood that this hypothesis has not been proved. Attempts to "synthesize" cytochrome b from protohemin and diphtheria toxin have thus far been without success. Diphtherial cytochrome b itself is not toxic and no attempt has been made as yet to cause its dissociation to a toxic component and hemin. Moreover, cytochrome b is not precipitated when tested with rabbit antitoxin serum. Nevertheless, we feel that the evidence which has been presented strongly suggests that the toxin is related to cytochrome b. If this is indeed the case, then it is conceivable that diphtheria toxin acts by blocking the synthesis of cytochrome b or some closely related enzyme in the susceptible animal. Such a theory must be regarded as speculative until further knowledge has been obtained concerning the nature and role of cytochrome b in normal and intoxicated animal tissues.

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## AMERICAN ASSOCIATION OF IMMUNOLOGISTS

### PRESIDENTIAL ADDRESS

#### SCIENCE, FREEDOM AND PEACE

Chicago, May 19, 1947\*

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Benjamin Franklin said that he looked forward to the day when a philosopher, transported to any land on earth, could say "This is my country." Franklin and the other scientists of his time, indeed, before his time, understood clearly that science, alone, of men's major intellectual interests, has no frontiers and no national varieties. The charter (1662) of the Royal Society of London, for example, provides that it may "enjoy mutual intelligence and knowledge with strangers and foreigners without any molestation, interruption, or disturbance whatsoever in matters philosophical, mathematical, or mechanical" and a similar statement with the proviso that it was to apply even in war was put into the charter (1780) of the American Philosophical Society.<sup>1</sup>

Today, nearly two centuries later, in a world

which, as someone has said, science has clearly made too small for war, we find these ideals even less attainable than they were in Franklin's time. The concept of total war, introduced and practised by the Germans, has deviated science from its high function of service to humanity, bent it to the invention of ever more effective means of man's destruction, and bound it to the will of the soldier and politician so that it is no longer free to communicate its knowledge. Indeed, the function of the scientist in war has become so all-pervasive that, were he to stand aside and have none of it, war would speedily revert to its early status of individual combat and personal prowess, and the world's literature might be enriched by a modern "Iliad" instead of a "Hiroshima."

What can you and I do toward the withdrawal of all scientists from the harmful uses to which their knowledge has been perverted? I say *all*, because such action would necessarily have to involve all scientists of all countries. "Impractical," you say? Perhaps, but not impossible, for scientists are trained to think and no one who thinks can avoid drawing back with horror at the

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<sup>1</sup> Conklin, E G, *Proc Amer Phil Soc*, 1947, 91, 1





AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS  
SYMPOSIUM ON CHEMISTRY AND METABOLISM OF NUCLEIC  
ACIDS AND THEIR CONSTITUENTS

INTRODUCTION

HUBERT S LORING, CHAIRMAN

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Most of the fundamental chemistry of ribonucleic acid was worked out on yeast nucleic acid before 1921 by the pioneer researches of Jones and Levene and their various collaborators. It was during this year that Levene advanced his theory of the tetranucleotide structure of ribo- and desoxyribonucleic acids. This theory was based fundamentally on the fact that under proper conditions four mononucleotides and only four could be isolated from nucleic acids. The proportion of the four bases making up the molecule as determined by direct isolation and by indirect methods indicated that some preparations gave values consistent with the tetranucleotide theory. A number of investigations on yeast nucleic acid provided conflicting evidence, but the tetranucleotide theory seemed well established for desoxyribonucleic acid and the ribonucleic acid of wheat germ. Confirmation of a tetranucleotide structure from diffusion measurements seemed also to have been obtained although Levene's idea as stated with Bass was that "the tetranucleotide theory is the minimum molecular weight and the nucleic acid may as well be a multiple of it." That this was, indeed, the case became evident from investigations made on the ribonucleic acid of the tobacco mosaic virus in comparison with that from yeast.

The finding that a nucleic acid was present in the tobacco mosaic virus greatly stimulated interest in nucleic acids. As other viruses were purified and found to contain nucleic acid, it was emphasized

again and again that this cell constituent played an important part in virus multiplication and growth. A fitting culmination of the idea of the importance of nucleic acids in relation to growth was the finding that the substance responsible for the transformation of an attenuated pneumococcal type into the fully encapsulated and virulent organism was, as nearly as could be determined, a desoxyribonucleic acid. The goal of a controlled chemical mutation long sought by the geneticist was thus achieved, although with a chemical of somewhat uncertain composition.

The great advances made in the field of chemotherapy have also stimulated nucleic acid research. If the growth of an undesirable bacterial contaminant can be controlled by the presence of a relatively harmless chemical, structurally resembling a metabolite essential for the bacteria, then a similar metabolic block may be possible in the reactions by which nucleic acid is synthesized. If such a chemical could be found, a fundamental approach to the problem of growth and the possible control of virus diseases might be provided.

I am sure it is with a similar optimistic outlook on nucleic acid research that the various lines of work to be presented in this symposium were undertaken. I believe the authors have approached their subjects in the spirit with which these symposia are organized namely to provide a free discussion of their current opinions.

# ENZYMATIC DEGRADATION OF RIBOSENUCLEIC AND DESOXYRIBOSE-NUCLEIC ACIDS WITH AN ADDENDUM ON THE EFFECT OF NUCLEATES ON THE HEAT STABILITY OF PROTEINS

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Because of the suggestive connection of nucleic acid with the structure of viruses and of chromosomes (cf (1)), with transmissible and inheritable changes in the morphologic pattern of certain bacteria (2), and with physiologic processes involving normal and atypical growth and development (3), considerable contemporary interest in this class of high-molecular-weight compounds has been evoked. Knowledge of the metabolic fate of the nucleic acids within tissues is of fundamental importance in the understanding of the phenomena presumed to be elicited by these substances.

On complete hydrolysis, the nucleic acids yield nitrogenous bases (purines and pyrimidines), sugar, and phosphoric acid. These three components are combined for the most part in the form of nucleotides within the nucleic acid molecule whereby the phosphoric acid is esterified with sugar, and the base is combined in either ribosidic (yeast) or desoxyribosidic (thymus) linkage. The nucleotides are combined with each other through phosphate ester linkages, phosphoric acid thereby being doubly esterified, and these nucleotide combinations are polymerized to yield molecules of high molecular weight.

Of the nitrogenous bases, three, namely, adenine, guanine, and cytosine, contain amino groups which possess the potentiality of furnishing ammonia on hydrolytic enzymatic desamination. Of these, only guanine is desaminated in most tissues. When combined in nucleoside or nucleotide linkage, the susceptibility to enzymatic desamination of guanine, of adenine, and to a more limited extent, of cytosine, is considerably increased. Nucleotides of each of the nitrogenous bases are readily dephosphorylated in extracts of most tissues by phosphatases to which the designation of nucleotidase has been applied. The polynucleotide combinations which form the molecule of nucleic acid are held together by phosphate ester linkages which may be hydrolyzed under certain conditions by polynucleotidase, an enzyme which because of the nature of the susceptible linkage may be classed as a phosphatase. The polymerized polynucleotides are held together by forces not yet understood. Enzymes presumably responsible for the desaggregation of the nucleic acid polymers have been designated as nucleodepolymerases (cf (1)). The designation nucleinase has frequently been applied to the enzyme complex concerned with the degradation of the intact and polymerized nucle-

ate to the individual nucleotides. The nucleinase complex includes, therefore, those systems referred to as depolymerase and polynucleotidase.

The enzymatic desamination of the individual bases, of the nucleosides, and nucleotides, and the enzymatic dephosphorylation of the nucleotides have often been investigated (4-6, cf (7)). Much less is known about the behavior under similar conditions of the more complicated molecules of the nucleic acids. Greenstein and Chalkley (8) studied the desamination at neutral pH of ribosenucleic and desoxyribosenucleic acids added to aqueous extracts of rat spleen and noted the following: 1) The rate of desamination of the nucleates is progressive with time, reaching a maximum value of 100 micrograms of ammonia nitrogen evolved from 5 mg. of either type of nucleate, 2) although in dialyzed, salt-free extracts of spleen, ribosenucleic acid is desaminated to the same extent as in fresh extracts, desoxyribosenucleic acid is not at all desaminated, 3) the capacity to desaminate the desoxyribosenucleate can, however, be completely restored to the dialyzed extract by adding at 0.01M concentration the sulfate, acetate, nitrate, or halide (except fluoride) of any one of the alkali or alkaline earth metals (except beryllium), the hydrochlorides of such bases as guanidine or arginine, and the chlorides of manganese, cobalt, and nickel, 4) the sodium salts of fluoride, bicarbonate, and phosphate not only fail to restore to the dialyzed extract the capacity to desaminate desoxyribosenucleate but also are inhibitory when added to the fresh extract, 5) within limits, the desamination of desoxyribosenucleate is markedly affected, that of ribosenucleate relatively little affected, by the degree of dilution of the fresh extract, a phenomenon which apparently has little to do with the level of salt concentration, 6) when dialyzed extracts of spleen are digested with ribosenucleate, much more phosphorus appears in dialyzable form than in fresh extracts of the tissue, and 7) the desamination of the nucleates by transplanted hepatomas is very much higher than that of normal liver.

It seems probable that the nucleates are split into smaller fragments during the digestion period (9), and that the ammonia may be derived from any one of these fragments, ranging from nucleic acid down to the free purine. It is not yet definitely established whether desamination precedes, accompanies, or follows the fragmentation by depol-



ymerase, polynucleotidase, the nucleotidases, or the nucleosidases. At the present time the designation nucleodesaminase can be applied only to the progressive appearance of ammonia in digests of nucleic acid with aqueous tissue extracts, without commitment as to the size or state of the substrate at any moment. Nucleodesaminase activity may thus be the sum of the activities of numerous individual desaminases, as well as a reflection of the net activity of one or more related enzymes, such as depolymerase and polynucleotidase, etc.

The designation nucleophosphatase activity can be given to the progressive appearance of inorganic phosphate in such digests, such designation being subjected to the same limitations as mentioned previously for that of nucleodesaminase. As will be noted from the data presented, the possibility that nucleic acid or its split products can function partly as a phosphate donor makes the picture of nucleophosphatase activity still more complicated (9).

#### ANIMAL TISSUES

The tissues of well over 2,000 rats and mice were employed for the present studies. The animals were killed by decapitation or cervical dislocation, and the tissues were freshly removed, ground in a glass mortar with clean sand, and then taken up in measured volumes of distilled water. After lightly centrifuging, the supernatant was used as the source of enzyme. All such extracts were used within a half hour after preparation.

For experiments with dialyzed extracts, the appropriate freshly prepared extract was divided into halves. One half was placed in a cellophane tube and dialyzed against frequently changed, distilled water for 24 hours within the ice box. The other half was kept in a glass container at the same temperature and for the same period. This fresh tissue control after standing for 24 hours at 5° C had very nearly the same activity as when it was newly prepared. Because of this consideration and in view of the fact that the reproducibility of the data from one tissue extract to another was as good as  $\pm 10$  per cent, the practice of setting up this fresh extract control was abandoned. In experiments with dialyzed extracts in which a nearly salt free condition was desired, it was found necessary also to dialyze the nucleate solutions. Desoxyribosenucleate is prepared in the presence of sodium chloride, and since it forms an inhomogeneous mass of fibers, the possibility cannot be excluded that certain samples may contain varying quantities of this salt despite efforts at purification. As noted later completely dialyzed mixtures of various tissues with dialyzed solutions of desoxyribosenucleate yield neither ammonia nor phosphate. If dialyzed mixtures do demonstrate the presence of these substances, it is found that either

extract or nucleate solution, or both, was insufficiently dialyzed.

#### SUBSTRATES

The nucleates employed were the soluble, purified sodium salts of yeast nucleic acid and of thymus nucleic acid. Samples of the latter type of nucleate were prepared by the method of Hammarsten (10). The yeast nucleate gave a phosphorus value of 80 per cent, the two thymus-nucleate preparations gave phosphorus values of 84 and 88 per cent. Less than 5 per cent of the nucleate preparations was dialyzable through cellophane.

Yeast nucleic acid serves as a model for the ribosenucleic acids and thymus nucleic acid for the desoxyribosenucleic acids. The terms "ribosenucleate" and "desoxyribosenucleate" used throughout this paper refer, therefore, to materials obtained from yeast and from the thymus gland, respectively.

#### ENZYME DETERMINATIONS

According to the method employed, 1 cc. of the desired extract was mixed with 1 cc. of substrate. The control consisted of 1 cc. of the same extract, together with 1 cc. of distilled water. After incubation at 37°C. for a specified period, ammonia nitrogen or phosphate phosphorus was determined in both test and control mixtures, and the difference in values found gave the amount of ammonia or phosphate released from the substrate. The substrate solutions were stable in every case and by themselves never liberated ammonia or phosphate, nevertheless, such solutions were never kept for more than a few days in the refrigerator.

The pH of the mixtures was stabilized by the natural buffers of the tissues and remained within the limits of 6.8 to 6.4 during the course of the experimental period. No added buffers were employed since it was apparently unnecessary and because it was desired to note the specific effects of ions on the enzymatic systems studied, particularly in dialyzed extracts. In only one case was the pH limit mentioned exceeded, and that was when bicarbonate was used in certain experiments. The pH in such mixtures was 7.8-8.0. Control experiments, made with extracts to which very dilute solutions of sodium hydroxide were added so as to yield the pH 7.8-8.0, demonstrated very little differences in enzymatic activity from those extracts at the lower pH. It can, therefore, be assumed that whatever effects were noted with the bicarbonate ion were due specifically to the ion and not to the difference in pH from that of the digest used for comparison.

#### DESAMINATION AND DEPHOSPHORYLATION OF PURINES, NUCLEOSIDES, AND NUCLEOTIDES

Before investigating the enzymatic splitting of nitrogen and phosphorus from the nucleic acids, it

was considered desirable to possess some information of these phenomena in digests containing the simpler components of the acids Table 1 lists data on purines, pyrimidines, nucleosides, and nucleotides in extracts of various tissues of the rat and of the mouse

Neither adenine nor cytosine (nor isocytosine) is desaminated by any of the tissues Of all the tissues studied, only mouse kidney, and to a very slight extent mouse liver, are capable of desaminating cytidine and cytidylic acid The desamination of cytidylic acid is accomplished by extracts

80 and 90 per cent of the ammonia and phosphate observed at 5 hours had been split off the substrates within the first hour There was relatively little difference between the values found after 15 and after 5 hours of incubation The impression was gained that most of the reaction occurred during the first hour of incubation, went just so far, and progressed very little after that, with no marked differences in rates of desamination and dephosphorylation Data obtained on dialyzed tissues did not vary significantly from those obtained on corresponding fresh extracts

TABLE 1

*Ammonia N and phosphate P evolved in digests of purines, pyrimidines, and nucleotides with fresh aqueous tissue extracts\**

TISSUE	SUBSTRATE											
	Adenine	Adenylic acid		Guanine	Guanosine	Guanylic acid		Cytosine	Cytidine	Cytidylic acid		Uridylic acid
	N	N	P	N	N	N	P	N	N	N	P	P
Rat												
Liver†	0	40	61	42	55	50	80	0	0	0	48	80
Kidney†	0	48	82	40	44	48	90	0	0	0	78	90
Spleen†	0	50	56	48	50	48	60	0	0	0	44	90
Brain	0	0	42	52	50	50	48	0	0	0	40	32
Pancreas	0	10	12	20	30	20	18	0	0	0	8	80
Muscle	0	0	0	0	40	40	24	0	0	0	0	62
Mouse												
Liver	0	48	56	40	44	46	50	0	>0	>0	52	80
Hepatoma 587	0	48	40	44	48	48	72	0	—	0	38	90
Kidney	0	50	84	50	48	46	84	0	30	40‡	84	90
Spleen	0	36	12	39	44	50	14	0	0	0	8	65
Brain	0	0	52	40	46	44	50	0	0	0	46	42
Pancreas	0	8	12	0	40	42	18	0	0	0	8	48
Muscle	0	0	0	0	44	40	30	0	0	0	0	22

\* Digests consisted of 1 cc aqueous extract (equivalent to 166 mg tissue) plus 1 cc of neutralized substrate solution containing respectively 124 mg adenylic acid, 045 mg adenine, 051 mg guanine 101 mg guanosine, 128 mg guanylic acid, 041 mg cytosine 085 mg cytidine 120 mg cytidylic acid, and 120 mg uridylic acid Incubation period was 5 hours at 37°C Results are given in ms of micrograms of ammonia N or inorganic phosphate P Values of 50 micrograms N or 112 micrograms P are those obtained, respectively on complete desamination or dephosphorylation  
 † Isocytosine was also resistant to enzymatic desamination  
 ‡ Dialyzed extracts of these tissues had very nearly the same desamination and dephosphorylation activity as did corresponding fresh extracts

§ Noted in mice of strains A, C C3H and dilute brown

of the kidneys of A, C, C3H, and dilute brown strain mice This species and organ specificity in regard to the desamination of cytidylic acid is indeed curious in view of the fact that all the tissues studied, except muscle, in both rats and mice, can dephosphorylate the pyrimidine nucleotide Guanylic acid is readily desaminated, and both guanylic acid and uridylic acid are readily dephosphorylated, all seemingly to a generally wider extent than is either adenylic or cytidylic acid The most active tissue generally is kidney, particularly that of the mouse

The data given in table 1 refer to values obtained after 5 hours of incubation Most of the substrates listed were studied after 05- and 15-hour incubation periods, and it was noted that between

#### DESAMINATION AND DEPHOSPHORYLATION IN MIXTURES OF NUCLEOTIDES

To some extent, as Loring and Carpenter recently showed, (11) ribosenucleate is composed of the four nucleotides, adenylic, guanylic, cytidylic, and uridylic acids For purposes of the present study, three sets of data were derived as follows Desamination and dephosphorylation were studied 1) on 5 mg ribosenucleate per cubic centimeter of substrate solution in fresh and in dialyzed tissue extracts, and 2) on equimolecular mixtures of the four separate nucleotides in such total concentration as to be equivalent per cubic centimeter to 5 mg ribosenucleate, e g, total weight 51 mg per cubic centimeter The data obtained were then compared 3) with the sum of

the ammonia and of the phosphorus split from each of the four nucleotides digested separately and independently in each extract, each nucleotide being at the same concentration as in 2) The data are given in table 2

For every tissue except kidney, the summation of the individual dephosphorylation of the nucleotides is the same in fresh and in dialyzed extracts and is greater than that of the nucleotide mixtures, which in turn is greater than that for ribonucleate in fresh extracts. Except for muscle, the extent of dephosphorylation of the nucleotide mixture is very much the same as that of ribonucleate in dialyzed tissue extracts. Like the case of each of the individual nucleotides, the desamination and dephosphorylation of the nucleotide mixture are also nearly complete during the first hour of incubation. It would appear that the splitting of phosphate when all four nucleotides are contained within a given volume is hindered, as compared with the splitting of each of the nucleotides when occupying individually the same volume. Whether each of the four nucleotides in the mixture is affected to an equal extent or whether one or more become resistant under such conditions cannot be answered at the present time. With the exception of liver and muscle, the desamination summation of the individual nucleotides is not different from that of the nucleotides mixture. In liver and in muscle extracts, the desamination of the nucleotide mixture is less than the desamination summation of the four individual nucleotides.

With the possible exception of the kidney, the dephosphorylation of the nucleates in fresh but not in dialyzed extracts falls considerably below those of the nucleotide mixture, and with the exception of both kidney and spleen, the same is true of the desamination phenomenon.

It is interesting that the most active tissue in dephosphorylating individual nucleotides, mixtures of nucleotides, or the nucleates, is the kidney. Mouse kidney in particular is also the most active in desamination of the nucleotides (no doubt because of its effect on cytidylic acid), sharing with spleen the most active desaminating effect on the nucleates.

#### EFFECT OF SALTS AND OF DIALYSIS

It was repeatedly noted in earlier experiments that dialyzed spleen extracts split off more dialyzable phosphorus from ribonucleate, but no more ammonia nitrogen, than did fresh extracts of this tissue (8). Under these conditions, dialyzed spleen extract split neither phosphorus nor ammonia from desoxyribonucleate. The addition of any one of a wide variety of salts to the dialyzed spleen extract restored the desamination capacity to act on desoxyribonucleate, but no further

tests were made for phosphorus in the presence of this substrate.

The effect of dialysis and the effect of the addition of a variety of salts to both dialyzed and to fresh extracts of a number of rat tissues are given in table 3.

The following points in table 3 may be noted: 1) Tissue extracts require salts for the metabolism of desoxyribonucleate but not for that of ribonucleate, 2) except in extracts of kidney, sodium bicarbonate and sodium fluoride have an

TABLE 2

Comparison of ammonia N and phosphate P evolved in digests of single nucleotides, of equimolar mixtures of 4 different nucleotides and of ribonucleate in fresh and in dialyzed tissue extracts\*

TISSUE	AMMONIA N AND PHOSPHATE P EVOLVED FROM—							
	Summation of 4 nucleotides† in fresh or in dialyzed extracts				Ribonucleate‡			
					Mixture of 4 nucleotides† in fresh or in dialyzed extracts		In fresh tissue extracts	
	N		P		N		P	
Rat								
Liver	90	269	44	106	20	55	56	124
Kidney	96	340	94	300	80	225	92	223
Spleen	98	250	90	52	96	25	96	65
Brain	50	162	50	60	32	10	42	70
Pancreas	30	118	30	60	0	0	0	78
Muscle	40	86	8	40	0	0	0	11
Mouse								
Liver (strain A)	94	268	62	140	16	25	—	—
Hepatos 587	96	240	60	120	50	60	—	—
Kidney	136	342	125	310	82	240	—	—

\* Incubation period was 5 hours at 37°C. Results are given in terms of micrograms ammonia N or inorganic phosphate P. Digests consisted of 1 cc tissue extract (equivalent to 166 mg tissue) plus 1 cc substrate solution.

† Represents sum of N or P evolved from individual digests of adenylic, guanylic, cytidylic and uridylic acids each at concentrations given in table 1.

‡ Represents N or P evolved from equimolar mixtures of adenylic, guanylic, cytidylic and uridylic acids, each acid at the same concentration as given in table 1. Results nearly identical in dialyzed tissues.

§ Concentration of nucleate was 5 mg per cubic centimeter.

inhibiting effect on the desamination and dephosphorylation of the nucleates whether in fresh or in dialyzed extracts, 3) dialyzed extracts of liver, spleen, brain, pancreas, and muscle produce more dephosphorylation of ribonucleate than do fresh extracts of these tissues, while dialyzed extracts of liver and of brain produce more desamination of this substrate, 4) dialyzed extracts of kidney plus salts produce more desamination of desoxyribonucleate but no more dephosphorylation than do fresh extracts, 5) dialyzed extracts of all the tissues neither desaminate nor dephosphorylate desoxyribose-

nucleate, 6) addition of the chlorides of sodium, potassium, calcium, magnesium, or arginine considerably enhances, beyond that of the fresh tissue, the capacity of the dialyzed extracts of liver to desaminate and dephosphorylate desoxyribosenucleate, and of spleen, brain, and pancreas to dephosphorylate this substrate, 7) addition of bicarbonate or fluoride to the dialyzed extracts of the tissues fails to restore either desamination or dephosphorylation capacity for desoxyribosenucleate, 8) all the effective chlorides appear to be nearly equally active in the degree to which each restores or enhances, beyond that of the fresh tissue, the desamination and dephosphorylation capacity of the dialyzed tissues, and 9) although

dialyzed extracts in the presence and absence of salts have been repeatedly confirmed

The requirement of the tissue extracts for the presence of salt in order to desaminate and to dephosphorylate desoxyribosenucleate (as contrasted with the apparent dispensability of salts in the desamination and dephosphorylation of ribosenucleate) can apparently be satisfied to an equal extent by a wide variety of monovalent and divalent salts. Experiments on the time course of the desamination of desoxyribosenucleate by dialyzed rat-spleen extract showed that the rate of reaction was very nearly the same in the presence of 0.0 M sodium chloride, magnesium chloride, or arginine monohydrochloride

TABLE 3

*Effect of salts on the desamination and dephosphorylation of nucleates in fresh and in dialyzed rat tissue extracts\**

SUBSTRATE†	SALT‡	LIVER				KIDNEY				SPLEEN				BRAIN				PANCREAS				MUSCLE			
		Fresh		Dialyzed		Fresh		Dialyzed		Fresh		Dialyzed		Fresh		Dialyzed		Fresh		Dialyzed		Fresh		Dialyzed	
		N	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P
Ribosenucleate	MgSO <sub>4</sub>	23	50	53	124	86	240	92	228	92	20	96	65	32	10	42	70	0	0	0	75	0	0	0	11
	NaHCO <sub>3</sub>	26	50	63	130	84	236	92	230	92	20	96	65	—	—	—	—	—	—	—	—	—	—	—	—
	NaF	7	40	10	14	74	250	88	240	43	10	14	18	—	—	—	—	—	—	—	—	—	—	—	—
	NaI	7	32	0	10	62	245	40	140	28	10	0	8	—	—	—	—	—	—	—	—	—	—	—	—
Desoxyribose-nucleate	NaCl	3	40	0	0	58	180	0	0	80	6	5	4	0	0	0	0	0	0	0	32	0	0	0	0
	KCl	6	40	20	110	58	200	102	210	80	6	86	160	0	5	0	25	0	5	0	32	0	0	0	0
	CaCl <sub>2</sub>	6	40	20	112	58	210	102	200	80	6	86	150	—	—	—	—	—	—	—	—	—	—	—	—
	MgCl	6	49	22	124	58	208	102	220	80	6	84	180	—	—	—	—	—	—	—	—	—	—	—	—
	Arginine HCl	6	50	24	156	58	220	104	220	84	8	90	210	—	—	—	—	—	—	—	—	—	—	—	—
	NaHCO <sub>3</sub>	6	45	20	120	58	210	100	195	86	6	92	200	—	—	—	—	—	—	—	—	—	—	—	—
	NaI	2	35	0	8	20	200	0	0	10	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	NaF	0	0	0	0	15	210	12	0	0	2	0	4	—	—	—	—	—	—	—	—	—	—	—	—

\* Digests consisted of 1 cc tissue extract (equivalent to 166 mg tissue) plus 1 cc substrate. Extracts were dialyzed for 24 hours against distilled water at 5°C. Salts added as 0.2 cc of 0.15 M stock solutions to extracts prior to mixing with substrate. Incubation period was 5 hours at 37°C. Results are given in terms of micrograms ammonia N and phosphate P.

† Substrates at concentration of 5 mg per cubic centimeter water. Substrate solutions used with dialyzed extracts were themselves dialyzed against water for 24 hours.

‡ In final concentration of 0.014 M in digests. Salts at concentrations higher than 0.5 M were inhibitory.

in the fresh-tissue extract the dephosphorylation of ribosenucleate exceeds that of desoxyribosenucleate, the reverse is true in dialyzed extracts of liver and of spleen.

These findings are generally consistent with those noted earlier on spleen (8) and by extension of the investigation to still other tissues have emphasized the phenomena. The considerably greater desamination and dephosphorylation capacity of dialyzed extracts of certain tissues for ribosenucleate and for desoxyribosenucleate (when salt is present) is noteworthy, particularly in view of the fact that the desamination and dephosphorylation of the individual nucleotides or of the equimolecular nucleotide mixture are practically the same in fresh and dialyzed extracts. These observations of fresh extracts and on

The inhibitory effect of bicarbonate and of fluoride on the enzymatic capacities of the tissues for the nucleates is also observed to a smaller extent in the case of the individual nucleotides. The interesting fact in regard to these particular ions in their relation to the enzymatic degradation of the nucleates is not only that they inhibit activity in the fresh extract but also that they fail to restore the activity of the dialyzed extract.

Earlier work (8) and the data in table 3 indicate that dialysis of a tissue extract results in a loss in the capacity of the extract to desaminate and to dephosphorylate desoxyribosenucleate. This capacity can be restored by the various salts listed (table 4). In the study on dialyzed spleen extracts (8), a wide range of salts, many of them not generally encountered physiologically, pos-

sessed the capacity of restoring to such extracts the ability to desaminate desoxyribosenucleate. In order to see whether the same salts also restore the dephosphorylating ability to such extracts, an investigation similar to those described was made. The data are given in table 4. The desamination data are from the earlier report (8).

It may be noted 1) that those salts effective in restoring to the dialyzed extract the ability to desaminate desoxyribosenucleate are also effective in restoring the dephosphorylation ability, and

TABLE 4

*Effect of salts of various kinds on restoration of capacity for desaminating and dephosphorylating desoxyribosenucleate in dialyzed rat spleen extract\**

SALT	AMMONIA N	PHOSPHATE P
	micrograms	micrograms
No salt	0†	2‡
Sodium fluoride	0	0
Sodium chloride	90	150
Sodium bromide	92	153
Sodium iodide	90	145
Sodium nitrate	90	160
Sodium sulfate	83	160
Sodium citrate	90	120
Sodium succinate	83	140
Sodium glutamate	89	200
Sodium acetate	86	180
Sodium nitroprusside	90	180
Sodium bicarbonate	0	0
Lithium chloride	92	190
Potassium chloride	90	185
Rubidium chloride	94	180
Cesium chloride	90	172
Beryllium sulfate	0	0
Magnesium chloride	90	210
Calcium chloride	94	200
Strontium chloride	92	190
Barium chloride	90	190
Manganese chloride	88	200
Nickel chloride	80	180
Cobalt chloride	82	180
Guanidine hydrochloride	94	190
Arginine hydrochloride	92	190

\* Digests and experimental conditions as in table 3.

† Value for fresh extract: 54 micrograms ammonia N.

‡ Value for fresh extract: 6 micrograms inorganic phosphate P.

2) that those salts that inhibit the restoration of the desaminating capacity also inhibit the restoration of the dephosphorylating capacity. The data in table 5 simply further emphasize the data in table 4, but the former show that even non-physiologic ions possess the ability to restore to the dialyzed extract the ability to metabolize desoxyribosenucleic acid.

#### ACID-SOLUBLE PHOSPHORUS IN DIGESTS OF NUCLEATES IN FRESH AND DIALYZED EXTRACTS

The data in table 5 show 1) that under otherwise similar conditions the total acid-soluble phos-

phorus formed from the nucleates in fresh extracts of rat spleen appears to be higher in the case of desoxyribosenucleate than of ribosenucleate, and in the case of the former substrate, higher in dialyzed, salt-containing extracts than in fresh extracts, 2) when this total acid-soluble phosphorus is corrected for by the amount of inorganic phosphate phosphorus present, the organically bound, acid-soluble phosphorus in the fresh tissue is still higher in the case of desoxyribosenucleate as compared with ribosenucleate, 3) in the dialyzed, salt-containing tissue relatively little organically bound, acid-soluble phosphorus is present, by far the greater proportion of the total

TABLE 5

*Acid-soluble phosphorus formed in digests of nucleates in fresh and dialyzed extracts of rat spleen\**

SUBSTRATE†	SALT‡	TOTAL ACID-SOLUBLE P		CORRECTED ACID-SOLUBLE P§	
		Fresh	Dialyzed	Fresh	Dialyzed
Ribosenucleate	NaHCO <sub>3</sub>	23	—	3	—
		23	20	13	2
Desoxyribosenucleate	NaCl MgCl <sub>2</sub> Arginine HCl NaHCO <sub>3</sub>	76	8	70	4
		100	170	94	10
		100	214	92	4
		94	210	88	10
		15	0	12	0

\* Digests consisted of 1 cc extract (equivalent to 186 mg tissue) plus 1 cc substrate. Extracts were dialyzed for 24 hours against distilled water at 5°C. Salts added as 0.2 cc of 0.15 M stock solutions to extracts prior to mixing with substrate. Incubation period was 5 hours at 37°C. At end of incubation period 1 cc of 5 per cent trichloroacetic acid was added to each tube; the mixture centrifuged and total P determined in supernatant. Results are given in terms of micrograms P.

† At 5 mg per cubic centimeter water.

‡ In final concentration of 0.014 M in digests.

§ Total acid-soluble P minus inorganic phosphate P. See table 3.

acid-soluble phosphorus being inorganic phosphate, and 4) dialysis of the extract or addition of bicarbonate has a decidedly inhibitory effect on the formation of both inorganic and organically bound, acid-soluble phosphorus. Comparison of the last two columns in table 6 suggests that the organically bound, acid-soluble phosphorus derived from the nucleates is split further in the dialyzed, salt-containing extract into inorganic phosphate. Thus the considerable rise in the amount of inorganic phosphate in digests of dialyzed extract with desoxyribosenucleate and salt is caused to a large extent by the splitting into inorganic phosphate of the acid-soluble, organically bound phosphorus produced from the nucleate. Not all the rise in inorganic phosphate level is accounted for in this way, and part of this

rise must have its origin in other sources, perhaps in the phosphorus of the acid-insoluble fraction. In the absence of added salt, little total acid-soluble phosphorus appears in the dialyzed extract. The effect of added salts may be to activate the formation of organically bound, acid-soluble phosphorus from which the inorganic phosphate is derived.

DESOXYRIBOSENUCLEOPOLYMERASE ACTIVITY

There is an enzyme present in tissues which catalytically effects a reduction in the extreme asymmetric shape of sodium desoxyribosenucleate (14). The activity of this enzyme can be conveniently followed by examining over the time interval of incubation the changes in those physi-

TABLE 6  
Effect of added sodium desoxyribosenucleate on the heat stability of crystalline egg albumin\*

NUCLEATE	PERIOD REQUIRED FOR COAGULATION
mg	minutes
Water	0.2
10	>120
5	>120
2.5	>120
1.25	>120
0.63	>120
0.31	>120
0.15	>120
0.08	0.2
0.04	0.2
0.02	0.2
0.01	0.2

\* Concentration of dialyzed protein solution was 6.6% and was brought to the pH of the nucleate solution, 6.8, with dilute NaOH. Mixture consisted of 1 cc. of protein solution and 1 cc. of either distilled water or dialyzed nucleate solution. Temperature 98°C.

cal properties of the nucleate which are the result of changes in its shape. Observation of the structural viscosity of solutions of the nucleate in ranges of velocity gradients where the viscosity changes are notably sensitive to changes in molecular asymmetry affords an excellent method of following the activity of the responsible enzyme system. Because the activity of the enzyme is measured by a physical property of the substrate which presumably is based upon a special state of molecular aggregation, the designation depolymerase was given to the enzyme, without commitment as to the mechanisms involved in its action or to the nature of the susceptible linkages within the substrate. In mixtures of tissue extracts with desoxyribosenucleate, the depolymerization of the substrate may be considered to be the primary step in its degradation. It is of some interest to see whether it bears any relation to

subsequent desamination and dephosphorylation reactions induced by other enzyme systems in the extract.

As noted in tables 3 and 4, dialysis of the extracts removes their capacity to desaminate and to dephosphorylate desoxyribosenucleate, but on

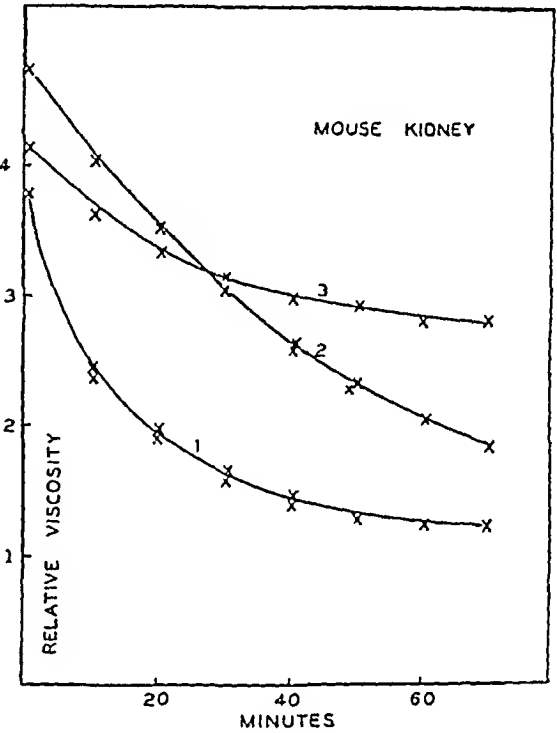


Fig 1 Relative viscosity at constant external pressure of 16 cm. water and at 30°C. of mixture of 3 cc. dialyzed 0.5 per cent sodium desoxyribosenucleate, 3 cc. aqueous extract of mouse kidney (at a concentration equivalent to 166 mg. tissue per cubic centimeter), plus 0.6 cc. of either water or 0.15 N salt solution. Curve 1 refers both to fresh tissue and to dialyzed tissue extract to which sodium chloride, magnesium chloride, or arginine monohydrochloride was added. Curve 2 refers to dialyzed tissue extract in the absence of added salt, curve 3 to dialyzed tissue extract in the presence of sodium bicarbonate. Ordinate, viscosity of mixtures relative to that of the extract; abscissa, period of incubation of the mixtures in the viscometer. Bingham-Jackson viscometers were employed.

addition to certain salts to the dialyzed extract this capacity can be restored. Although numerous salts are included among these restorative salts, sodium bicarbonate and sodium fluoride are not (table 3). In order to note the activity of the depolymerase for sodium desoxyribosenucleate under these conditions, viscosimetric studies of various mixtures incubated in the viscometer were made. They are illustrated in figure 1.

Figure 1 shows that the progressive, enzymatic depolymerization of the nucleate is slowed in the dialyzed extract as compared with the fresh extract, but it apparently is not prevented. Addition of sodium chloride, magnesium chloride, or arginine monohydrochloride in final concentration of 0.015N restores the activity of the depolymerase to that found in the fresh extract. Under conditions whereby desamination and dephosphorylation of the substrate are completely prevented, namely, in the salt free, dialyzed extract, depolymerization of the substrate can, nevertheless, take place, even if at a somewhat slower rate than that in the fresh extract. It may be that the inert, nonenzymatic proteins in the dialyzed extract exert a weak, activating effect on the depolymerase, an effect considerably augmented when certain inorganic or organic salts are added. It is apparently possible to have some depolymerase activity in the absence of any desamination or dephosphorylation. It may therefore be assumed that the substrate aggregates of lower asymmetry, formed as a result of the action of depolymerase, do not yield ammonia or phosphate in the absence of salt and that the presence of such salt is even more crucial to those subsequently acting systems which produce organically bound, acid soluble phosphorus (table 4) and perhaps to the activity of the desaminases and dephosphorylases than to the activity of the depolymerase. Bicarbonate added to the dialyzed tissue extracts does not restore the capacity of such extract to desaminate or to dephosphorylate desoxyribosenucleate, and as noted in figure 1, it inhibits the depolymerase in the dialyzed extract.

Sodium chloride, magnesium chloride, and arginine monohydrochloride are equally effective in restoring the full capacity of the dialyzed extract to depolymerize the desoxyribosenucleate (fig. 1) as well as in producing in such digests organically bound, acid soluble phosphorus and in freeing ammonia and phosphate. This catholicity in effect by so many diverse salts is remarkable. The fact that the restorative effects of certain salts appear to be connected with so many phenomena involved in the metabolism of desoxyribosenucleate suggests either that these effects are specific at one crucial stage in the early breakdown of this substrate or that the degradation products bear some family resemblance among themselves in their reaction to the presence of such salts.

The most obvious thing to note in the studies herein described is the fact that extracts of different tissues affect the desamination and dephosphorylation of the nucleates to different extents. On the one hand there is the kidney which desaminates and dephosphorylates the nucleates to a very large extent, and on the other hand there

are pancreas and muscle which do not affect these substrates to any appreciable extent. Between these extremes there are spleen, which desaminates considerably and dephosphorylates very little, liver, which both desaminates and dephosphorylates relatively little, and brain, which affects only ribosenucleate and that to a very slight extent. Yet even the tissues ineffective on the nucleates, e.g., muscle, pancreas, and brain, desaminate and dephosphorylate the free nucleotides, susceptible purines, and nucleosides, and nucleotide mixtures to a relatively smaller extent than do the more active tissues it is true. It may be that extracts of muscle, brain, etc., do not degrade the nucleates to particles the size of susceptible free nucleotides. On the whole, it appears probable that the nucleotide phosphatases and nucleotide desaminases are not generally active on the nucleates or their early degradation products and are distinct from those systems responsible for the desamination and dephosphorylation of the nucleates or their immediate split products.

After dialysis, and in the presence of salts, extracts of liver desaminate and dephosphorylate the nucleates more than do fresh extracts, extracts of spleen, pancreas, and brain dephosphorylate the nucleates more than do fresh extracts, while extracts of kidney do not desaminate or dephosphorylate the nucleates any more than do the fresh extracts of this tissue. The enormous increase in the inorganic products in digests of desoxyribosenucleate with dialyzed tissues takes place only in the presence of a wide variety of salts and does not occur either in the absence of salt or in the presence of such salts as fluoride or bicarbonate. The reason why dialysis does not increase the desamination and dephosphorylation of nucleates in extracts of kidney or the desamination of nucleates in the extracts of spleen may be due to the possibility that these substrates are already desaminated or dephosphorylated to the nearly maximum extent in the respective fresh tissues. Apparently when in the fresh tissue the desamination proceeds to the extent of 100 micrograms and the dephosphorylation to 200-300 micrograms per 5 mg. of nucleate, dialysis of the tissue causes no augmentation of enzymatic degradation of ribosenucleate, in the case of desoxyribosenucleate in the presence of effective salt, only a restoration of the degradation takes place to an extent characteristic of the fresh tissue. In extracts of liver, where the desamination and dephosphorylation capacity is originally low, and in spleen, where dephosphorylation is initially low, it is possible by dialysis and salt treatment procedures to enhance the desamination and dephosphorylation above that observed in the respective fresh tissues.

It would appear that something is removed from extracts of liver, spleen, brain, etc., on dialysis,



which permits the further appearance of inorganic phosphate and ammonia and which, conversely, in the fresh extract inhibits in some way the appearance of these products. In such tissues as designated, dialysis does not apparently affect the desamination and dephosphorylation of simple nucleotides or of mixtures of nucleotides.

There are two possible explanations as to the differences observed in certain tissues in the fresh and in the dialyzed state. One may be based upon the assumption that in the fresh extract of liver or spleen there is some inhibitor for dephosphorylation and desamination which is removed by dialysis. The second explanation may be based upon the assumption that there is some acceptor for phosphate and for ammonia which is present in fresh extracts of liver or of spleen and which likewise is lost on dialysis. According to the latter explanation, the nucleic acids or their larger split products but not the nucleotides may function as phosphate and ammonia donors. To what recipients this phosphate may be donated is not known. According to either explanation, extracts of kidney possess neither an inhibitor for dephosphorylation nor a system capable of accepting phosphate from nucleic acid.

The data in table 5 indicate that the increase in inorganic phosphate in the dialyzed extracts is at the expense of the organically bound, acid-soluble phosphorus formed in the digest of nucleic acid. For this purpose, in the case of desoxyribosenucleate the presence of salts is required. Sodium chloride, magnesium chloride, and arginine monohydrochloride are equally effective in this respect, whereas sodium bicarbonate is toxic. It would appear as if salt were essential under these circumstances in order to degrade the desoxyribosenucleate into acid soluble fractions which in the dialyzed but salt-treated extract break down further to yield inorganic phosphate.

Bicarbonate does not inhibit the dephosphorylation of either ribosenucleate or desoxyribosenucleate in fresh extracts of kidney, or the dephosphorylation of ribosenucleate in dialyzed kidney extract. It does not restore the dephosphorylation of desoxyribosenucleate in the dialyzed extract of the kidney. If there were an inhibitor for dephosphorylation of nucleates in fresh extracts of other tissues, it would be difficult to believe that it could be solely bicarbonate.

The fact that the amount of phosphate phosphorus is higher in dialyzed extracts of liver and of spleen indicates that the enzymes responsible for the degradation of the nucleates in these tissues are not necessarily weaker than those in the kidney, but simply that conditions in the fresh extracts of the two former tissues are such that except by dialysis the full potentiality for the break-down of the nucleates in such tissues

is not realized. Whether such conditions in the fresh tissue consist of the presence of an inhibitory, interfering system or of an accepting system for phosphate cannot be definitely answered at the present time. Further research is needed to elucidate this point.

The comparison in rates of desamination and dephosphorylation of individual nucleotides, of nucleotide mixtures, and of the nucleates, each group at equivalent concentration (table 2), suggests that the lowered values in the case of the mixture of nucleotides as compared with the summation of the individual nucleotides are the result of competitive inhibition in digests involving the nucleotide mixture. The ribosenucleate incubated in fresh tissue extracts yields ammonia and phosphate in even lower amount than does the nucleotide mixture but the values found in nucleate digests with dialyzed tissues approximate those noted for the nucleotide mixture. In more concentrated tissue extracts of kidney and spleen, the dephosphorylation of ribosenucleate and of the nucleotide mixtures is very nearly the same. In dialyzed extracts of liver, kidney, and spleen, ribosenucleate acts as if it was a mixture of four ribosenucleotides in equivalent proportions. There is no difference in desamination and dephosphorylation of the ribosenucleotide mixture in fresh or in dialyzed extracts, but there is in the case of the ribosenucleate. Whatever interferes in the fresh extract with the desamination and dephosphorylation of ribosenucleate must act upon the latter in a stage higher than that of the mononucleotide.

The very considerable differences in conditions necessary to derive ammonia and phosphate from desoxyribosenucleate as compared with ribosenucleate are shown by the data in tables 3 and 5. The wide variety of salts effective in the degradation of desoxyribosenucleate is particularly impressive and as contrasted with ribosenucleate offers the possibility of regulating the metabolism of the desoxyribosenucleate by regulating the salt level. There is apparently little specificity among the effective salts, monovalent metal cations being as effective as monovalent organic cations and divalent metal cations. The ions need not even be commonly physiologic, for as earlier shown ((8) and table 4) such ions as lithium, cesium, rubidium, strontium, and barium were as active as sodium, magnesium, or calcium, while sodium glutamate was as active as arginine hydrochloride. The fact that the desamination and dephosphorylation of desoxyribosenucleate is strongly influenced also by the concentration of the extract suggests that the nonenzymatic proteins of the extract may also exert an activating influence on the metabolism of this substrate. The dialyzed tissue extract is still

capable of desaminating and dephosphorylating ribosenucleate but loses the capacity to affect desoxyribosenucleate. The capacity to restore, and in some tissues to exceed the normal level of desaminating and dephosphorylating desoxyribosenucleate can be effected by the wide variety of salts mentioned. It seems probable, therefore, that although desamination and dephosphorylation may not be directly related in the fresh extract, they may be indirectly related by virtue of being mutually dependent upon a common state of the desoxyribosenucleate arrived at in the presence of effective salt. Furthermore, the fact that the same wide range of salts, some physiologic and some nonphysiologic, some inorganic and others organic, can restore to the dialyzed extract the capacities for both desaminating and dephosphorylating desoxyribosenucleate, and the further fact that the same salts (fluoride, bicarbonate) do not restore the capacity for either desaminating or dephosphorylating suggests that the salt effect is concerned with the activation of the enzymatic degradation of the nucleate to a form that can be both desaminated and dephosphorylated. The possibility must be envisaged that the appearance of ammonia and inorganic phosphate in the digests described may be secondary to that enzymatic degradation of the nucleates for which any one of an extensive variety of salts is required. It is difficult to see how or why so many diverse salts affect in equal manner such different processes as desamination and dephosphorylation. Nevertheless, the problem at what precise point or points in the enzymatic break down of desoxyribosenucleate the need for salts occurs remains for future investigation.

The inhibitory effect of the bicarbonate and of the fluoride ions is difficult to understand, for these ions not only are inhibitory in the fresh extract but also are nonrestorative in the dialyzed extract. It is possible that they either participate in competing reactions or lack the necessary dimensions to combine effectively with the specific enzyme protein in order to activate it.

Fresh extracts of the various tissues show very decided differences among themselves in their capacity to desaminate and dephosphorylate the two types of nucleates, kidney being by far the most active. Since in the dialyzed extracts of liver and spleen, the amount of phosphate observed tends to increase and approach the value noted in the kidney extracts, it would appear that the differences between such tissues as liver, spleen, and kidney tend to diminish when the extracts of such tissues are dialyzed and then treated with effective salts (table 3). This observation is reminiscent of that made by Chalkley and Greenstein (15) in the determination of the decolorization rates of methylene blue in fresh and dialyzed

extracts of liver and of hepatoma. The rates of decolorization of the dye in the presence of nucleates were found to be different in fresh extracts of the two tissues but were nearly the same in dialyzed extracts of these tissues. It might appear that the differences in nucleic acid metabolism noted in fresh extracts of various tissues are due for the most part to dialyzable components in these tissues and that when such components are removed by dialysis, the activity values for the various tissues tend to approach each other. These findings emphasize the fact that when one measures enzymatic activity in a fresh tissue extract or homogenate, what is being measured is not necessarily the true activity or the concentration of the enzyme but the net effect of all conditions present in the material being studied. The limiting factor under these conditions may not be the enzyme itself, and the result of measuring certain products of the reaction may be simply to yield a reflection of concomitant and sometimes competing reactions and thus no exact picture of the primary reaction.

In fresh-tissue extracts, the desamination and dephosphorylation of ribosenucleate invariably exceeded that of desoxyribosenucleate. In dialyzed extracts of liver and of spleen and in the presence of effective salts, the level of dephosphorylation of desoxyribosenucleate exceeded that of ribosenucleate.

There seems to be little doubt that during the course of the digestion of either type of nucleate in tissue extracts degradation of the nucleate takes place which leads to fragments sufficiently small to pass through a cellophane membrane (less than 10,000 in molecular weight based on a spherical molecule). At what stage in the fragmentation desamination and dephosphorylation begin is not yet known. From the data in the present paper, it seems probable that the enzymes concerned with the desamination and dephosphorylation of the nucleotides may not be the same as those concerned with the production of ammonia and inorganic phosphate from the nucleic acids or presumably their higher split products. An analogy may be drawn from the metabolism of proteins in which a complex of proteases and peptidases is concerned, each enzyme acting in a specific manner upon the substrates of different size and configuration. An entire range of polypeptides of different sizes can apparently be attacked by such a complex proteolytic system as crude trypsin, and the designation of such terms as "aminopeptidase" and "carboxypeptidase" refers not to the size of the polypeptide substrate but only to the point of attack by the enzyme. The rate limiting factor in the break down of protein by the crude proteolytic system would be the activity of the primary protease reaction, but

this in turn would be influenced by the rate at which the products of the reaction were removed. Without belaboring the analogy unduly, it may be hypothesized that some similar complex mechanism is operative in the case of the enzymatic degradation of the nucleic acids, fragmentation, desamination, and dephosphorylation taking place alternately and concurrently as the digestion proceeds.

The maximum inorganic phosphate split from ribosenucleate in extracts of rat kidney amounts to 60-80 per cent of the total nucleic phosphate. The ammonia split under the same conditions in extracts of rat kidney or spleen amounts to 60-70 per cent of the total amino nitrogen in the ribosenucleate, and in extracts of mouse kidney to 90 per cent of the total amino nitrogen. The difference in desamination in extracts of rat or mouse kidney must be due to the capacity of the latter tissue to desaminate the cytidylic acid moiety. It would seem probable that extracts of rat kidney and spleen desaminate only the adenylic acid and guanylic acid moieties while those of mouse kidney desaminate the moieties of all three aminated nucleotides. Mouse-kidney extracts apparently effect close to the maximum desamination and dephosphorylation of ribosenucleate. The relatively close concordance of the Fiske-Subbarow and Lowry-Lopez methods of phosphate estimation suggests that the greater part at least of the inorganic phosphate measured in the digests with nucleates actually represents phosphate split from the substrates enzymatically and not a product that is the result of hydrolysis of acid-labile phosphate esters by the reagents used in the former determination.

#### ADDENDUM ON THE PROTECTIVE EFFECT OF DESOXYRIBOSENUCLEATE ON THE HEAT COAGULATION OF PROTEINS

In connection with the enzymatic experiments described above, it was noted (8) that whereas aqueous extracts of various tissues immersed in boiling water produced almost immediately a coagulum of protein, such extracts previously treated with sodium desoxyribosenucleate (Hammarsten) did not yield a coagulum even after many hours of heating at 100°C and remained quite clear. It appeared that the nucleate exerted a protective action on the proteins of the extract and increased their thermal stability beyond the capacity of any agent known at present. Studies on one of the most labile of proteins, namely crystalline egg albumin, are shown in table 6 (16).

It is interesting to note that there is a sharp break in the concentration range of nucleate effective in conferring complete protection against heat coagulation. At this point, somewhere between 0.15 and 0.08 mg of nucleate, roughly

1 mg of the nucleate will prevent the heat coagulation of about 600 mg of egg albumin. It is probable that below this critical concentration of nucleate, some proportion of the protein molecules is not coagulated by heat, because the turbidity of solutions containing these lower concentrations of nucleate is not quite as great as in the absence of this substance.

That there is some stoichiometric relation between the concentration of protein and of nucleate was revealed by repeating the experiments mentioned in the tabulation with an albumin solution half as concentrated. With this diluted solution of protein, 0.08 mg of nucleate

TABLE 7  
*Thermal stability at 38°C of egg albumin in the presence of  
desoxyribosenucleate and sodium chloride.\**

NUCLEATE	SODIUM CHLORIDE	PERIOD REQUIRED FOR COAGULATION
mg	mg	minutes
Water	Water	0.2
10	Water	>120
10	9	0.2
10	6	0.2
10	3	0.2
10	2	>120
10	1	>120
0.15	Water	>120
0.15	9	0.2
0.15	6	0.2
0.15	3	0.2
0.15	2	>120
0.15	1	>120
Water	9	0.2†
Water	6	0.2†
Water	3	0.2†
Water	2	0.2†

\* Concentration of protein, 0.6 per cent. Mixtures consisted of 1 cc protein solution plus 1 cc of either distilled water or thymus nucleate plus 1 cc either distilled water or sodium chloride.  
† Heavy coagulum.

was effective in inhibiting heat coagulation whereas 0.04 mg of nucleate was ineffective.

Different preparations of sodium thymus nucleate were used, each with varying degrees of polymerization. The results were identical throughout. In order to prove finally that the degree of polymerization of the nucleate was unimportant in the effect noted, a solution of one preparation of the nucleate was divided into two aliquots. One aliquot was irradiated at 2537Å for several hours until the viscosity greatly diminished. Both aliquots were then used as in the foregoing with identical results. Even with the highly polymerized Hammarsten preparations, the lower, still effective concentrations, are barely more viscous than water.

The experiments were performed in the absence of added salt. Data involving the use of added salt prior to heating are given in table 7.

The data in table 7 reveal that the protective action of thymus nucleate is still obtained under the present conditions when 2 mg or less of sodium chloride is present. Above this concentration of salt, heat coagulation of the protein occurs whether 0.15 or 10 mg of nucleate is present. The critical concentration of sodium chloride, about  $3-4 \times 10^{-5}$  mols, is thus apparently independent of the nucleic concentration. Addition of salt after heating and subsequent cooling yields no coagulation. Reheating of this mixture results in a gel.

Very few sulfhydryl groups are liberated in the protein on heating under these conditions, whether nucleate is present or not. Indeed, the amount

and then cooled. There was no evidence of coagulation. Addition of desoxyribonuclease and magnesium ions, and incubation for a short period of time resulted in flocculation and precipitation of the proteins of the extract (table 8). Addition of desoxyribonuclease alone, or magnesium alone failed to show this effect. Ribonuclease was also ineffective. There seems to be no doubt but that the intact desoxyribonucleate fibres hold the denatured protein in some kind of homogeneous medium, and that when the nucleate is disaggregated by its specific nuclease, it loses this property. That the forms of depolymerization induced by ultraviolet radiation (which is still effective in preventing protein coagulation) and by desoxyribonuclease— $Mg^{++}$  (which has lost this property) are entirely different is apparent from these results. Ultraviolet radiation opens up no new groups, whereas the nuclease action produces new acid groups (9).

TABLE 8

Substance added to Mixture \*

	PERIOD FOR COAGULATION AT 37 C
	minutes
Desoxyribonuclease and 0.003 M magnesium <sup>++</sup>	15
Desoxyribonuclease	>1440
Magnesium <sup>++</sup> (0.003 M)	>1440

\* 1 cc of desoxyribonuclease containing 0.1 mg purified enzyme protein added to mixture. Magnesium sulfate added as 0.05 cc of 0.15 M solution. The mixture consisted of 1 cc rat-liver extract (equivalent to 166 mg tissue), and 1 cc of 0.5 per cent sodium thymus nucleate. The mixture was heated for 30 minutes at 95°C with no appearance of coagulum and then cooled.

that appears, although giving a faint nitroprusside test, is too small for accurate quantitative measurement.

In contrast with the striking effect of desoxyribonucleate, ribonucleate employed under similar conditions is completely ineffective in preventing the heat coagulation of egg albumin. Agar is likewise ineffective. That it is the intact form of the desoxyribonucleate which is the effective agent, intact in the sense that while it may be highly polymerized or considerably depolymerized, no primary chemical bonds have released, is shown by the fact that after digestion with the specific desoxyribonuclease of McCarty, the nucleate is no longer effective (16). This is illustrated by the following experiment. An aqueous extract of liver was heated for 30 minutes at 95°C in the presence of desoxyribonucleate,

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# HYDROLYSIS OF RIBONUCLEIC AND DESOXYRIBONUCLEIC ACIDS WITH PHOSPHOESTERASE FROM CALF INTESTINAL MUCOSA

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The phosphoesterase preparation from calf intestinal mucosa can hydrolyze both diesters and monoesters of phosphoric acid at alkaline pH values (1, 2, 3). This enzyme preparation, for example, hydrolyzes ribonucleic acid to mononucleotides, thus functioning as a diesterase, the mononucleotides in turn are hydrolyzed to nucleosides and phosphoric acid. The last step is effected by a monoesterase, which is more generally known as alkaline phosphatase. We will use the term phosphoesterase to include both the diesterase and monoesterase of preparations from calf intestinal mucosa. Our own studies (1) and those of Schmidt and Thannhauser (4) suggest that the hydrolysis of both diesters and monoesters of phosphoric acid by preparations from intestinal mucosa is probably effected by a single enzyme. The specificity of this phosphoesterase is apparently even broader, for the recent paper of Winnick (5) indicates that amides of phosphoric acid are hydrolyzed by this enzyme also.

The phosphoesterase of the intestine may function principally in the disposal of foods. It appears, however, to be identical with the alkaline phosphatase of blood and tissues, the importance of this enzyme is attested by its involvement in many physiological processes, as recently reviewed by Moog (6).

We have been interested principally in the ability of the enzyme in the intestinal mucosa to hydrolyze nucleic acid to mononucleotides, that is, to function as a diesterase. This reaction must be important from a physiological standpoint. In addition, it has been possible to perform the hydrolysis quantitatively, which has given information bearing on the structure of the nucleic acids. Klein, as recently as 1941 (7), pointed out that there was no satisfactory method for determining phosphodiesterase (polynucleotidase). Klein suggested the use of a titrimetric procedure to measure acid groups released or the procedure of Levene and Dillon (8) which compared the release of phosphoric acid from nucleic acid and from simple monoesters of phosphoric acid. We have found that the manometric procedure devised by Bain and Rusch (9) for determining ribonuclease could be utilized for the diesterase. Measurement of the enzyme by this procedure is based on the release of  $\text{CO}_2$  from a bicarbonate medium at a slightly alkaline pH value by the secondary phosphoric acid groups which are formed by the action of the enzyme. The diesterase could be estimated also from

the increase in solubility of the substrate nucleic acid in the uranium reagent (uranium acetate in trichloroacetic acid), a procedure which was used by Kunitz (10) for determining ribonuclease. Both of these methods were satisfactory with either ribonucleic acid or desoxyribonucleic acid (nuclease-treated) (3) as the substrate, but we have used principally the manometric procedure because of its convenience.

Ribonuclease, which is a highly specific phosphodiesterase, and the enzyme from intestinal mucosa, a non-specific diesterase, can be distinguished by the lability of the latter to heat (4). Study of the optimum concentration of substrate required by the phosphoesterase (1) has revealed another important distinguishing difference which is shown in figure 1. The phosphoesterase is optimally active with small concentrations of ribonucleic acid, whereas ribonuclease requires a relatively high concentration. We have utilized (11) this difference for estimating the concentration of these two enzymes in various tissues by comparing the reactivity with 150 and 5 mg of ribonucleic acid in a volume of 3.5 cc. The data obtained with the purified enzymes are shown in figure 2. A comparison of the activity of the tissues with 150 and 5 mg of nucleic acid showed that non-specific phosphoesterase was abundant in intestinal mucosa and kidney, the latter containing this enzyme almost exclusively, whereas pancreas, which is rich in ribonuclease, contained little of the non-specific phosphoesterase. This procedure has limitations and a better method might be to use nuclease-treated desoxyribonucleic acid (3) as the substrate for the phosphoesterase. So far, the phosphoesterase is the only enzyme known to hydrolyze this nucleic acid to mononucleotides.

Because of the ability of the phosphoesterase to hydrolyze small concentrations of nucleic acid, it can be utilized for quantitative hydrolysis of the nucleic acids. The course of hydrolysis measured manometrically at pH 8.14 is shown in figure 3 (2). Curve A was obtained with 4.0 mg of ribonucleic acid, Curve B with 2.0 mg. These data must be corrected for retention of  $\text{CO}_2$  due to carbonate ion and buffers and for the dilution effect on addition of the enzyme. With the best nucleic acid preparation 0.85 equivalent of acid was released by hydrolysis for each atom of phosphorus or 3.4 per tetranucleotide residue (four phosphorus). The corrections mentioned above were negligible in experiments performed at pH 7.62, but adenosine

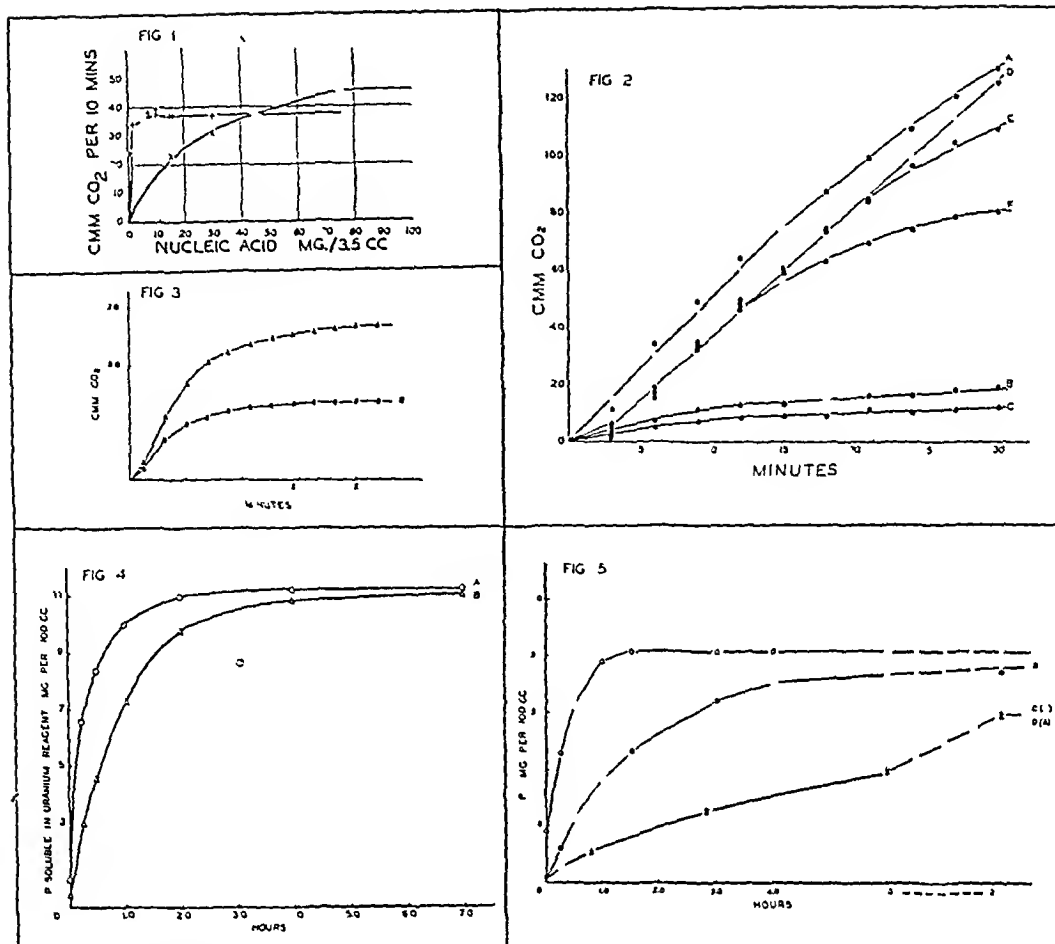


Fig 1 Activity of ribonucleinase and phosphodiesterase with various concentrations of ribonucleic acid Ribonucleinase (v) 10% of enzyme with 10 cc of 0.1 M NaHCO<sub>3</sub>, an atmosphere of 5 per cent CO<sub>2</sub> — 95 per cent N, pH 7.5, total volume 3.5 cc Phosphodiesterase (+) same conditions with 0.4 cc of a 1 per cent solution, the optimum activity of this enzyme lies above pH 7.5

Fig 2 Action of ribonucleinase and non specific phosphodiesterase with several concentrations of ribonucleic acid in terms of CO<sub>2</sub> evolved from NaHCO<sub>3</sub> buffer Curve A, Ribonucleinase, 12%, with 150 mg ribonucleic acid, Curve B, with 5 mg ribonucleic acid, Curve C, with 3 mg ribonucleic acid Curve D, Phosphodiesterase, 2.0 mg, with 150 mg ribonucleic acid, Curve E, with 5 mg ribonucleic acid, Curve F, with 3 mg ribonucleic acid Each flask contained 1.0 cc of 0.1 M NaHCO<sub>3</sub>, nucleic acid, and the enzyme in the side arm

Fig 3 Evolution of CO<sub>2</sub> by the action of phosphodiesterase on various concentrations of ribonucleic acid 4.0 mg of enzyme were used in each experiment under the conditions employed for the

determination of the activity (2) Ribonucleic acid, mg, Curve A, 4.0, Curve B, 2.0

Fig 4 Enzymatic hydrolysis of ribonucleic acid measured by solubility in uranium reagent and liberation of inorganic phosphate 750 mg of nucleic acid were dissolved in 30.0 cc of water and 12.0 of 0.1 M NaHCO<sub>3</sub>, the pH was about 8.2 24.0 mg of the enzyme in 5.0 cc of water were added Total P in final solution = 0.11 mg per cc Samples were taken at the intervals indicated and mixed with an equal volume of uranium reagent The precipitate was removed by centrifuging and total P (Curve A) and inorganic phosphate-P (Curve B) determined on the supernatant fluid by the method of King

Fig 5 Action of phosphoesterase on untreated and nuclease treated desoxyribonucleic acid 30.0 cc of a 0.6 per cent solution of nucleic acid were buffered with 3.0 cc of 0.5 M NaHCO<sub>3</sub> and enzyme added (15.0 mg to the treated and 60.0 mg to the untreated nucleic acid) in a volume of 10.0 cc The experiments were performed at room temperature Immediately after adding enzyme, and subse-

deaminase, which was present in the enzyme preparation (12), was active at this lower pH and low values were obtained. When the data were corrected for the ammonia released by deamination or when the deaminase was inhibited by silver nitrate, the results were of the magnitude obtained above. Titration experiments in the range of secondary phosphoric acid groups gave slightly higher results than the manometric procedure.

The presence of more than three secondary phosphoric acid bonds per tetranucleotide residue is most in accord with the formula proposed by Levene for ribonucleic acid (13), a simple straight chain structure repeating the tetranucleotide unit, however, would not account for the specificity of ribonuclease which hydrolyzes only about one-third of ribonucleic acid and yet releases all four of the mononucleotides. Fletcher, Gulland, and Jordan (14) have postulated a formula for a tetranucleotide of ribonucleic acid which contains a triester of phosphoric acid. Complete hydrolysis of a polynucleotide containing this structure would release one primary and three secondary phosphoric acid groups for each four phosphorus atoms. The manometric procedure would not differentiate between a secondary and a primary phosphoric acid group, but the titration experiment which measures only secondary phosphoric acid groups seems definitely to exclude such a structure.

The action of the enzyme preparation on ribonucleic acid was also followed by determining the solubility of the nucleic acid in the uranium reagent and by the release of inorganic phosphate, the former being a measure of diester hydrolysis, the latter a measure of monoester hydrolysis. The course of hydrolysis is shown in figure 4 under conditions that gave complete hydrolysis in less than 7 hours at pH 8.0 and 22° (2). The early lag of the inorganic P at about one-half the value of the total uranium reagent soluble P probably represents the difference in the rates of hydrolysis of purine and pyrimidine nucleotides, the former being more rapidly hydrolyzed than the latter (15). We have not accurately determined the optimum pH for diester and monoester hydrolysis but both are above pH 8.

Similar experiments were performed with desoxyribonucleic acid prepared by the method of

Hammarsten (16). In figure 5 (3) are shown the increases in total P soluble in the uranium reagent, (Curve A) and in phosphate-P (Curve B) with a preparation of nucleic acid that had first been treated with the specific nuclease from pancreas, the nuclease recently purified by McCarty (17). Treatment of desoxyribonucleic acid with the nuclease, which has been reported to convert it to tetranucleotides (18), caused it to become completely soluble in HCl, whereas only a small portion was soluble in the uranium reagent, as shown in figure 5. This may be a true solubility of tetranucleotides in the uranium reagent and not a formation of some mononucleotides since precipitation of several different concentrations of nucleic acid has given about the same amount of P remaining in solution.

Experiments with nucleic acid that has not been treated with nuclease have shown that the phosphoesterase will hydrolyze it also, although more slowly and only to the extent of about 70 per cent. In figure 5 Curves C and D show the hydrolysis obtained. The phosphoric acid is split off as fast as mononucleotides are formed. Four times as much enzyme was used in this experiment as in the experiment for Curves A and B. Neither additional enzyme nor greater time gave complete hydrolysis. However, successive action of nuclease and phosphoesterase on this resistant fraction afforded complete hydrolysis, nuclease alone was not sufficient, hence there appears to be more than one bond remaining unhydrolyzed after the initial treatment by phosphoesterase.

The above finding is contrary to reports that phosphoesterase will not act on desoxyribonucleic acid in the native state, but the difference in resistance to hydrolysis appears to be quantitative and not qualitative. We feel that our phosphoesterase preparation does not contain nuclease, which might give the result observed by us, since proteolytic enzymes are used in its preparation and nuclease is readily destroyed by them. Further, the hydrolysis we have observed is not inhibited by sodium citrate, whereas the nuclease is inhibited by this reagent. Our substrate is highly polymerized in the sense of its being a satisfactory substrate for the nuclease as will be seen later. The divergent results may be due to a difference in the degree of non-specific, non-enzymatic depolymerization (19), but our results indicate that the bonds hydrolyzed by the nuclease may be intact and yet the phosphoesterase can bring about considerable hydrolysis. In view of the broad specificity of the phosphoesterase it is not surprising that it can hydrolyze a part of the desoxyribonucleic acid molecule, but the bond acted on by the nuclease appears not to be broken by this enzyme.

Quantitative manometric experiments were performed (3) with desoxyribonucleic acid similar to

quently at intervals, a sample was taken and mixed with an equal volume of uranium reagent. The precipitate was removed by centrifuging and total P and inorganic phosphate-P determined on the supernatant fluid. Nuclease-treated nucleic acid (total P = 0.320 mg/cc) Curve A, total soluble P, Curve B, inorganic phosphate-P. Untreated nucleic acid (total P = 0.288 mg/cc) Curve C, total soluble P, Curve D, inorganic phosphate-P.



those already described for ribonucleic acid. The specific nuclease released acid groups from desoxyribonucleic acid which we measured by the manometric technique, the amount of acid released was 0.81 of the amount calculated for one acid group for each four P atoms. This is an approximate agreement with the conclusions of Fischer and co-workers (18) that one group was released. Recent titra-

tion data of Carter and Greenstein (20) gave a value of 0.78 equivalent for each four P atoms.

Phosphoesterase was allowed to act on the nuclease-treated nucleic acid and the acid formed was measured manometrically. On the basis of total P 2.5 acid groups were released for each four P atoms. This value was raised to three if the calculation was based on uranium reagent-insoluble P. Con-

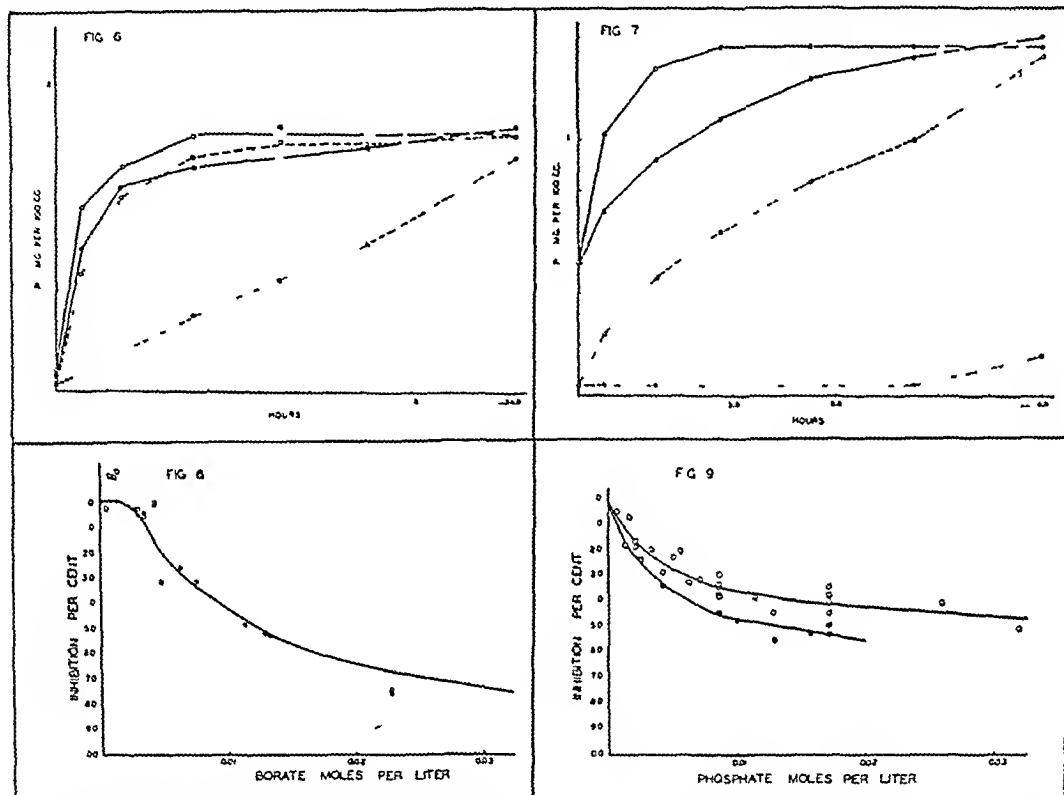


Fig 6 Enzymatic hydrolysis of ribonucleic acid, measured by increase in uranium reagent-soluble P and phosphate P, with and without sodium arsenate present. 75 mg of nucleic acid were dissolved in water and 2.4 cc of 0.5 M NaHCO<sub>3</sub>. Approximately 10 mg of the phosphoesterase preparation were added. The final total volume was 47.0 cc. Total nucleic acid P = 0.100 mg per cc. Samples were taken, treated with uranium reagent and analyzed. Another portion of nucleic acid was handled in the same way with sodium arsenate present (0.00213 M). O, without arsenate, ●, with arsenate. —, uranium reagent-soluble P, - - -, phosphate P.

Fig 7 Enzymatic hydrolysis of desoxyribonucleic acid, measured by increase in uranium reagent-soluble P and phosphate P, with and without sodium arsenate present. Nucleic acid that had been nuclease-treated was used. The amount of phosphoesterase used was only one-fifth of that

used in the experiments for Fig 6, otherwise the conditions were the same. Total P = 0.136 mg per cc. O, without arsenate, ●, with arsenate. —, uranium reagent-soluble P, - - -, phosphate P.

Fig 8 Effect of borate on the hydrolysis of ribonucleic acid by phosphoesterase. The manometric experiments were performed at pH 8.14 as described (2). Sodium tetraborate (borax), adjusted to pH 8.1, was placed in the bottom of Warburg flasks to give the final concentrations shown and the enzyme (about 1 unit (2)) introduced from the side arm. The results are corrected for the retention of CO<sub>2</sub> by borate. O, concentration of nucleic acid 20 mg per 3.5 cc, ●, concentration of nucleic acid 4 mg per 3.5 cc.

Fig 9 Effect of phosphate on the hydrolysis of ribonucleic acid by phosphoesterase. The conditions are the same as for Fig 8. O, concentration of nucleic acid 20 mg per 3.5 cc, ●, concentration of nucleic acid 4 mg per 3.5 cc.

firmatory data were obtained from titrimetric experiments. The data from nuclease and phosphoesterase experiments are consistent for a formula for this nucleic acid in which the mononucleotides are bound to each other through secondary phosphoric acid groups, one of which is hydrolyzed by the nuclease and the remaining three of which are hydrolyzed by phosphoesterase.

In the course of our studies we used desoxyribonucleic acid prepared by the method of Levene (21) in which hot 1.25 N NaOH is utilized. To our surprise this preparation of nucleic acid was not acted on by the specific nuclease (22), 15 per cent of this preparation of nucleic acid was soluble in 0.25 N HCl initially, in contrast with complete insolubility of nucleic acid prepared by the method of Hammarsten, but its solubility even after prolonged action of the nuclease did not exceed 20 per cent. It was observed also that this nucleic acid, when subsequently acted on by the phosphoesterase preparation at pH 7.62, although it was hydrolyzed to the same degree as the nucleic acid prepared by the method of Hammarsten, was not deaminated by the adenosine deaminase which the phosphoesterase preparation contains (12). This suggests that the adenosine had been altered, perhaps deaminated, by the strong alkali used in preparing the nucleic acid, or, since phosphoesterase alone cannot completely hydrolyze desoxyribonucleic acid, that adenosine had not been liberated. Desoxyribonucleic acid deaminated by the use of nitrite, which has been successfully used to deaminate ribonucleic acid (23), would be of interest in this connection. This deamination procedure would probably not degrade the nucleic acid molecule to the degree that alkali does.

Klein (24) found that the hydrolysis of mononucleotides to nucleosides by an enzyme preparation from intestinal mucosa could be inhibited by sodium arsenate, whereas the formation of the nucleotides from nucleic acid was not affected. Klein utilized arsenate with this enzyme preparation to prepare mononucleotides of desoxyribonucleic acid. We have found that the formation of the mononucleotides was inhibited by arsenate to some degree also. This led us to follow (25) both stages of the hydrolysis to determine the conditions under which the maximum concentration of mononucleotides would be obtained, the formation of mononucleotides has been followed by the increased solubility of the products in the uranium reagent and the formation of nucleosides by the appearance of phosphoric acid. The hydrolysis of ribonucleic acid with and without arsenate is shown in figure 6. The data show that the enzymatic break-down of the mononucleotides of this nucleic acid is inhibited much more than their formation. This would not be, however, an efficient procedure for obtaining these mononucleotides

and, fortunately, they can be obtained by hydrolysis of the nucleic acid with alkali at a suitable pH value (26).

The hydrolysis of desoxyribonucleic acid (nuclease-treated) under the same conditions used with ribonucleic acid but with one fifth as much enzyme is shown in figure 7. With this nucleic acid, the hydrolysis of the mononucleotides by phosphoesterase is almost completely prevented by arsenate. In the case of desoxyribonucleic acid the pyrimidine nucleotides can be obtained by acid hydrolysis but not the purine nucleotides because of the lability of the desoxyribose under the conditions required for their hydrolysis. Fortunately, the mononucleotides can readily be prepared by enzymatic hydrolysis and the conditions for obtaining a good yield with arsenate present can be seen from figure 7.

Klein (24) believed that arsenate was inhibitory to the hydrolysis of mononucleotides because of the resemblance of arsenate to phosphate, a product of the reaction which is inhibitory by competition with the substrate. We have not studied this stage of the hydrolysis but in the case of the formation of the mononucleotides manometric experiments have shown that arsenate is not inhibitory by competition with the substrate, since the percentage inhibition is the same for several different concentrations of nucleic acid.

The striking difference in the effect of arsenate on the release of phosphoric acid from the mononucleotides of ribonucleic and desoxyribonucleic acids had been observed by Klein. He states that the effect of arsenate on the hydrolysis of glycerophosphate and hexosediphosphate is negligible and that ribonucleotides stand between these compounds and desoxyribonucleotides. Sizer (27) who studied the effect of oxidants and reductants on the enzymatic hydrolysis of a number of phosphoric acid esters, none of them mononucleotides, found that sodium arsenate was not inhibitory to a phosphatase prepared from bovine lung tissue, which is in agreement with Klein's observations.

We reported recently (28) that borate was inhibitory to both the diesterase and monoesterase activity of the phosphoesterase preparation. It was suggested that the inhibition might be due to the interaction of borate with a polysaccharide component of this enzyme, the interaction of borate with simple carbohydrates being well known. The inhibition of the diesterase has been studied manometrically in detail with ribonucleic acid as the substrate. The results obtained, after correction for the large retention of  $\text{CO}_2$  by borate, are shown in figure 8. The first part of the curve where there is no inhibition may be due to the known interaction of the borate with a component of the enzyme preparation other than the enzyme, which might reduce the effective concentration of the borate. Two different concentrations of nucleic acid were em-

ployed, 20 and 4 mg per 3.5 cc, the percentage inhibition for a given concentration of borate was the same for each, indicating that inhibition was not by competition with the substrate. These results with borate were confirmed by experiments in which the activity of the enzyme was measured by increase of the solubility of the nucleic acid in the uranium reagent. We have found also, as shown in figure 9, that phosphate is inhibitory to the diesterase, an effect that is well known for the monoesterase (alkaline phosphatase). In this case, however, the inhibition increases with decrease in the concentration of substrate, which suggests that competition with the substrate probably is the

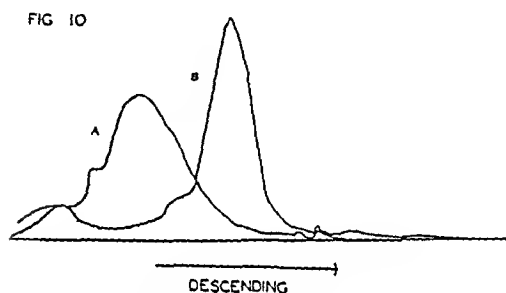


Fig 10 Electrophoresis patterns of a fraction from the phosphoesterase preparation. Electrophoresis was performed in phosphate and borate buffers pH 7.6, containing 0.15 M NaCl, ionic strength 0.2. Movement is toward the positive pole. Curve A: Descending pattern after 4.06 hrs. electrophoresis at 5.1 volts  $\text{cm}^{-1}$  in phosphate buffer. The mobility of the principal component is  $2.32 \times 10^{-3} \text{ cm} \cdot \text{volt}^{-1} \text{ sec}^{-1}$ . Curve B: Descending pattern after 4.63 hrs. electrophoresis at 5.7 volts  $\text{cm}^{-1}$  in borate buffer. The mobility of the principal component is  $3.62 \times 10^{-3} \text{ cm} \cdot \text{volt}^{-1} \text{ sec}^{-1}$ .

cause of the inhibition, as has been found with the monoesterase.

The explanation of the effect of borate on the phosphoesterase must await the preparation of the enzyme in pure form, but it is thought that the effect might be specific and perhaps indicate an interaction of borate with a polysaccharide component of the enzyme. It would be of interest to determine the effect of borate on cholinesterase which has been reported to be a polysaccharide-containing enzyme.

We have also reported the effect of borate in decreasing the solubility of the phosphoesterase preparation in ammonium sulfate (28). This effect is specific and borate cannot be replaced by phosphate. The most noticeable interaction of the borate is with an apparently non enzymatic component obtained by repeated precipitation by half saturation with ammonium sulfate in the presence

of borate (28), this material contained only 1 unit (2) of diesterase activity per 10 mg and contained 31.5 per cent of polysaccharide. At pH 7.6 the electrophoretic mobility of this material is greater in borate than in phosphate, as shown in figure 10, and a 5 per cent solution in borate is extremely viscous. The ability of the borate to interact with protein polysaccharide complexes and thereby reduce, differentially, their solubility in ammonium sulfate has made possible a fractionation of the phosphoesterase preparation. This procedure will no doubt be applicable to other protein polysaccharide complexes and perhaps to polysaccharides as well. Tissue polysaccharides have been little studied and the interaction of borate with them should be of interest. The work of Pfeiffer and co-workers (29) and others has shown that in borate poisoning there is a concentration of borate in the brain and liver. There may be polysaccharides in these tissues capable of binding borate similar to those which we have encountered in the intestinal mucosa.

#### SUMMARY

1. A phosphoesterase preparation from calf intestinal mucosa hydrolyzes both diesters and monoesters of phosphoric acid, hydrolysis of the latter being a measure of alkaline phosphatase. It is possible that a single enzyme carries out both reactions. Methods are described for determining the diesterase, using ribonucleic acid as the substrate and for differentiating between this non specific phosphodiesterase and ribonucleinase.

2. The secondary phosphoric acid groups released by phosphoesterase from ribonucleic acid have been measured manometrically and titrimetrically. The same methods have been used to measure the acid groups released from desoxyribonucleic acid by a specific nuclease and subsequently by the phosphoesterase, although the phosphoesterase was found to partially hydrolyze desoxyribonucleic acid without the intervention of the nuclease.

3. The effect of arsenate on the hydrolysis of both nucleic acids to mononucleotides and subsequently to nucleosides is described. In the case of desoxyribonucleic acid complete inhibition of the latter stage by arsenate provides a method for obtaining mononucleotides of this nucleic acid.

4. The diesterase is inhibited by borate and phosphate. With phosphate inhibition appears to be by competition with the substrate but with borate some other mechanism must be involved, perhaps interaction with a polysaccharide component of the enzyme.

5. Interaction of borate with one polysaccharide rich component of the phosphoesterase preparation has been demonstrated electrophoretically and by an increase in viscosity. This interaction of

borate and polysaccharide, which has been useful for purifying the enzyme, may be also of more general importance

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## INVESTIGATIONS ON THE BIOSYNTHESIS OF PYRIMIDINE NUCLEOSIDES IN *NEUROSPORA*<sup>1</sup>

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The principles involved in the utilization of artificially induced mutants for studies on mechanisms of biological syntheses and metabolism have now been firmly established. The general subject and the specific application of the mutants of the bread mold *Neurospora* to such problems have been reviewed by Beadle (1, 2). The series of reactions in figure 1 will serve to illustrate the principles involved.

If compound C is necessary for the growth of the organism and it is synthesized through the intermediates A and B, a mutation in gene 2 will result in a lack of ability to carry out reaction 2, probably due to a deficiency of the corresponding enzyme. The organism, therefore, will fail to grow unless compound C is supplied from the external environment. If the mutation is in Gene 1, growth can be initiated by either compound B or C. Thus unknown mechanisms of intermediary metabolism can be elucidated by investigations of mutants concerned in such a series of reactions. In some cases

such investigations are facilitated by accumulation of an intermediate before the genetic block and these intermediates can be isolated and identified.

*Mutations concerned with nucleic acid metabolism* Mutations concerned with nucleic acid have been found in considerable numbers among those induced in *Neurospora* (3, 4). A similar series has been isolated by Fries (5) in the mold *Ophiostoma*.

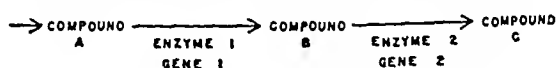


Fig 1 The relation of gene mutation to biochemical syntheses

*multiannullatum* Specific requirements of these mutants are listed in figure 2. No mutants have been found that utilize cytosine or thymine.

*Pyrimidine requiring mutants* In the group of 380 mutants of *Neurospora* described by Beadle and Tatum (3), 43 were found to require the nucleoside uridine or certain related compounds. It is not pertinent at this time to present the genetic analyses of this group in detail. However, certain of the genetic findings are essential for the development of the scheme of biosynthesis to be pre-

<sup>1</sup> This work was supported by grants from the Rockefeller Foundation and the Nutrition Foundation.

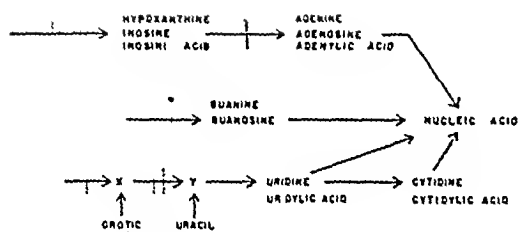


Fig 2 Mutations involved in ribonucleic acid synthesis. The broken lines indicate known different genes. \* Found in *Ophiostoma* but not in *Neurospora*.

sented. Three genetic types have been found so far and, as shown in figure 3, all three genes are

mally promotes a reaction in amino acid metabolism that is of the same type as the one lost by gene 2.

Although strains 2, 4 and 5 evidently represent mutations of the same gene they are physiologically quite different as shown in figure 3B. Number 2 like 1 and 3 requires uridine over the whole normal temperature range of wild-type *Neurospora*. On the other hand strain 4 does not require uridine in the lower temperature range. Strain 5 superficially appears to be like 2 but it is temperature sensitive with respect to its uridine requirement since at 25°C it requires only about one tenth as much uridine as the non temperature sensitive mutants. It has been demonstrated that this strain is able to synthesize most of its uridine require-

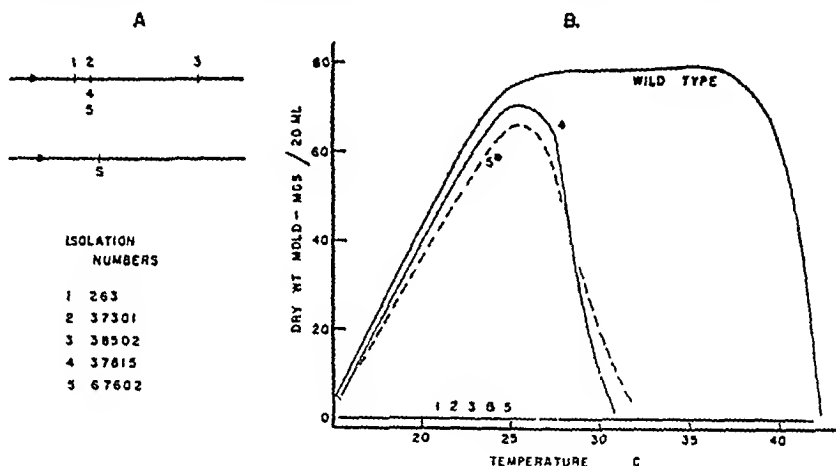


Fig 3 A Chromosome loci and isolation numbers of five uridine requiring mutants of *Neurospora*. B Temperature sensitivity of mutants 4 and 5. The broken line (5\*) refers to mutant 5 in the presence of 0.04 mg of uridine per 20 ml of medium. This is an insufficient quantity of uridine for more than 10% maximum growth of the non-temperature sensitive mutants 1, 2 and 3.

located on the same chromosome. In addition it has been indicated that two other mutants, numbers 4 and 5 in the figure, carry genes that are alleles of type 2. This has been indicated through two lines of evidence. First, crosses among these three strains produce only mutant progeny. Second, through spontaneous mutation a gene S (suppressor) became altered so that it took over the physiological function of the gene of type 2. Hence a strain carrying genes 2 and S, both in the mutant form, is able to grow in the absence of uridine. A like result is obtained with S in combination with the mutant gene of strain 4 or 5. On the other hand S does not affect the uridine requirement of strains 1 and 3. It is of interest to note that the amino acid arginine inhibits the action of S while histidine is stimulatory. The significance of these effects by the amino acids has not been determined but it may be suggested that the wild-type gene S nor-

ment at 25°C if a small amount of the nucleoside is supplied. It is probable therefore that the three strains 2, 4 and 5 carry stable mutations of the same gene that have definite and markedly different degrees of activity. These mutants with partial blocks can be utilized directly in studies of metabolism as will be shown later.

**Pyrimidine biosynthesis.** It was shown by Loring and Pierce (6) that *Neurospora* mutants utilized uracil and cytosine very poorly compared to uridine and cytidine and these investigators suggested that the cytosine at least does not occur as a normal intermediate in nucleic acid biosynthesis. This appears to be true for uracil also. A quantitative relation in utilization of uracil and uridine is shown in figure 4. Uracil is evidently utilized through an adaptive system and if sufficient time is allowed it is nearly as effective as the nucleoside

Orotic acid is utilized in a similar fashion by the strain that it affects

If cytosine and uracil are not normal intermediates, perhaps the ring is built directly on the ribose molecule with the formation of intermediate aliphatic glycosides. Some possible intermediates are shown in figure 5. Compound I could be the immediate aliphatic precursor of uridine. Compound II is suggested on the basis of the fact that orotic

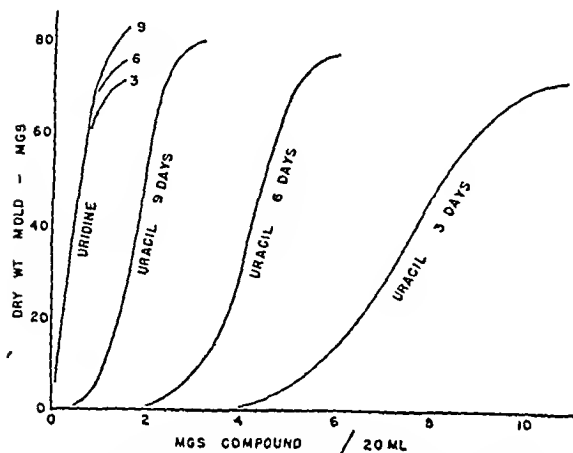


Fig 4 Utilization of uracil compared to uridine by non-temperature sensitive strains of *Neurospora*

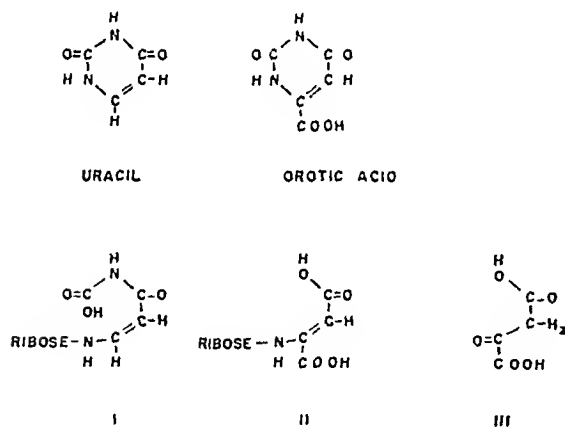


Fig 5 Some suggested intermediates in uridine biosynthesis

acid can promote the growth of only one of the three genetic types of pyrimidine mutants. This could logically arise from compound III, oxalacetic acid.

That oxalacetic acid is actually a precursor of uridine is suggested by the following data. Oxalacetic acid and some of its derivatives were synthesized and tested on all of the mutants. They were found to be ineffective in promoting the growth of strains 1, 2 or 3. This however is not surprising since a block in the synthesis of oxalacetic

acid would be expected to result in a multiple deficiency rather than just one for uridine. The genetic blocks 1, 2 and 3 must therefore come after oxalacetic acid synthesis. Consequently the mutants with partial blocks were utilized for testing.

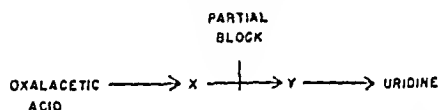


Fig 6 Use of mutants with partial blocks for investigating mechanism of metabolism

	RELATIVE REQUIREMENTS
<chem>OC(=O)CC(=O)O</chem> OXALACETIC ACID	12
<chem>NC(=O)C=C(N)C(=O)N</chem> AMINOFUMARIC ACID DIAMIDE	10
<chem>NC(=O)C=C(N)C(=O)O</chem> AMINOFUMARIC ACID	10
URACIL	1
PYRUVIC ACID	50
cerenic ACID	] >100
derable ACID	
spora (3), ACID	
Fries (5) ACID	
COMP ACID	
ASID	
ASID of g	

Fig 7 Compound promoting growth of the uridine requiring mutants that have partial blocks

the compounds. As indicated in figure 6 compounds coming in a series before a partial block could cause increased growth simply by mass law effect. A high requirement is to be expected in such a case. The compounds listed in figure 7 have been tested on strains 4 and 5 and rated in requirement for maximum growth relative to uracil.

From the data in figure 7 it is evident that oxalacetic acid and the derivatives tested, produce a specific and considerable effect on the mutants with partial blocks in pyrimidine synthesis

in view of the probable biological lability of the expected intermediates

The action of the suppressor gene S in bypassing the reaction controlled by gene 2 is of considerable

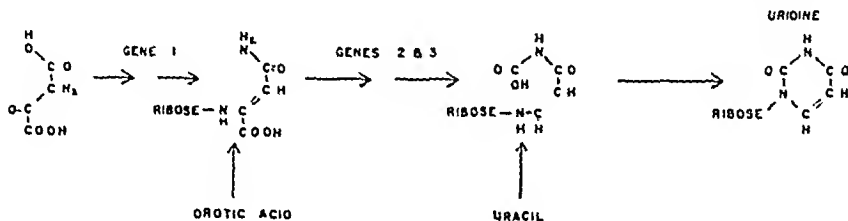


Fig 8 A suggested general mechanism for the biosynthesis of uridine from oxalacetic acid, orotic acid or uracil

The evidence that has been presented may be interpreted in terms of a general mechanism for biosynthesis of uridine in *Neurospora* similar to that given in figure 8

#### DISCUSSION

Although the activity of orotic acid on only one genetic type of the *Neurospora* pyrimidineless mutants and the activity of oxalacetic acid and its derivatives on the mutants with partial blocks makes the scheme of biosynthesis in figure 8 entirely reasonable it is possible that the oxalacetic acid serves only as a source for the carbonyl group in position 2 of the pyrimidine. In order to further establish the source of the carbon chain of the pyrimidine, investigations are under way on the preparation of oxalacetic acid with C<sup>14</sup> in position 2. The C<sup>14</sup> should thus be incorporated directly into the pyrimidine ring by the mutants with partial genetic blocks. In addition some progress has been made in the direction of synthesis of the proposed intermediates. It should be noted that none of the mutants of this series thus far investigated has shown any tendency to accumulate any of the intermediates of biosynthesis. This is not surpris-

ing. However, since the specific functions of genes S and 2 are not yet known, a further discussion must await further experimentation

#### SUMMARY

The production and specificity of artificially induced mutants of *Neurospora* that are involved in nucleic acid metabolism are reviewed briefly

Evidence is presented to indicate that the carbon chain of pyrimidines arises from oxalacetic acid. It appears that uridine is formed biologically through formation of intermediate aliphatic derivatives of ribose

Orotic acid may be substituted for uracil for one of three genetic types of pyrimidineless mutants of *Neurospora* though it is probable that neither pyrimidine is a normal precursor of uridine

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# THE ASSAY OF RIBONUCLEIC ACIDS FOR PYRIMIDINE RIBONUCLEOSIDES AND RIBONUCLEOTIDES<sup>1</sup>

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While the tetranucleotide theory<sup>2</sup> for yeast ribonucleic acid has been accepted for many years, there are a number of publications which provide evidence to the contrary. One such, for example, has indicated that there may be 1.8 times as much

lated as barium salts was only about 35 per cent of that required by the tetranucleotide theory (2). While such widely divergent results may be explained in part on the basis of the questionable purity of the products analyzed, it has seemed to us

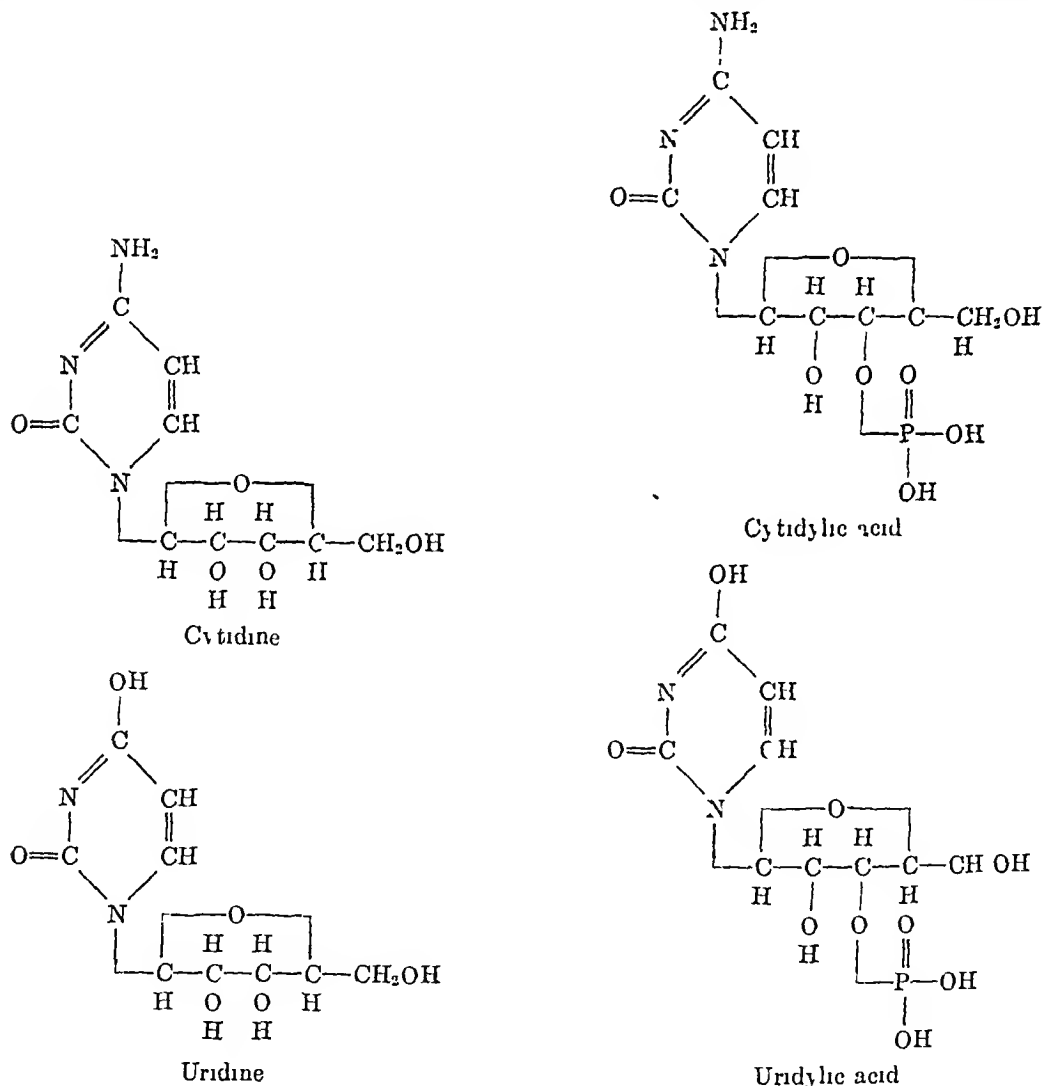


Figure 1

guanine present as adenine (1). In another the amount of pyrimidine nucleotides which was iso-

more likely that they may represent true differences in ribonucleic acid composition.

<sup>1</sup> Aided by a grant from the Rockefeller Foundation.

<sup>2</sup> Used without relation to molecular size but in the sense that the four mononucleotides are present in equimolar quantities.

The difficulty has rested for the most part on the absence of quantitative methods of analysis for the purine and pyrimidine components, particularly in nucleoside or nucleotide form. The *Neurospora* mutant developed by Beadle and Tatum, which was shown to require the pyrimidine nucleosides

or nucleotides for growth (3) has provided us with a method of assay for the pyrimidine components. Guanine may be determined by means of the phenol reagent (4) and adenine may be determined by the use of another *Neurospora* mutant (5). The application of these methods has made possible a better determination of the composition of ribonucleic acids. The preliminary results on their application to yeast nucleic acid and to tobacco mosaic virus nucleic acid indicate that in neither case do the values for the purine and pyrimidine components approach those of a statistical tetranucleotide.

Whereas the growth requirements of this strain, No. 1298, were determined by measuring the rate of progression of mycelium on an agar medium, we have found for assay purposes that a higher degree of reproducibility could be obtained in liquid culture. The structures of the pyrimidine ribonucle-

otides of precision obtained when concentrations of supplement are used which give less than half-maximum growth is relatively high. The standard deviation in five replicate determinations, for example, each at an average mycelium weight of 15.5 mg was 0.1 mg corresponding to values of cytidine of  $0.21 \pm 0.01$  mg.

As it is possible to hydrolyze ribonucleic acid either to the nucleotide or the nucleoside stage, the total pyrimidine nucleotide or nucleoside content can be determined, with some qualifications I shall mention later, directly on the hydrolysates obtained. As it is desirable as well to know the ratio of the two, we have investigated the fractionation of cytidine from uridine and cytidylic acid from uridylic acid and have found 12-phosphotungstic acid (6) a valuable reagent for this purpose. The amino compounds form nicely crystalline salts which are highly insoluble in acid solution in con-

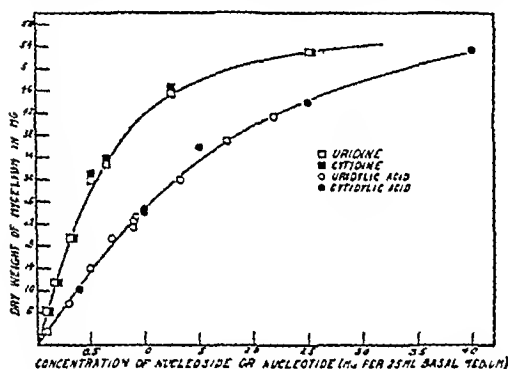


Fig 2 Growth curve of mutant strain No. 1298 on  $\square$ , uridine,  $\blacksquare$ , cytidine,  $\circ$ , uridylic acid, and  $\bullet$ , cytidylic acid

osides, cytidine and uridine and the ribonucleotides, cytidylic acid and uridylic acid, required for growth are shown in Figure 1. As maximum growth is obtained on any one of these compounds, it is evident that the mold can accomplish the necessary modifications for the formation of its own ribonucleic acid.

The growth response on cytidine and uridine and on the nucleotides is shown in Fig. 2, where the dry weight of mycelium obtained after 72 hours at  $25^\circ$  is plotted against concentration. It may be seen that the growth rate on the nucleosides in liquid culture like that found previously on an agar medium is greater than that on the nucleotides. In liquid culture, however, the rate on the two nucleosides is the same. The two nucleotides give the same curves although at the lower level as shown. While the rate of growth up to about half maximum is approximately linear and can be given with an accuracy of from 5 to 10 per cent by a straight line relationship, the use of the curve itself probably leads to slightly more precise values. The de-

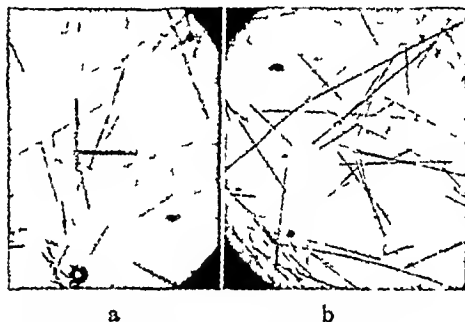


Fig 3 a Cytidine phosphotungstate b Cytidylic acid phosphotungstate (Mag 100  $\times$ )

trast to the oxy pyrimidines which because of the absence of basic groups do not form salts. Photomicrographs of cytidine and cytidylic acid phosphotungstates are shown in Figures 3a and 3b. As these compounds have not been prepared previously, the analytical data and empirical formulas are shown in Table I. Both compounds give analyses which indicate that two molecules of cytidine or of cytidylic acid are combined with one of phosphotungstic acid.

The respective solubilities of the two salts in acid solution at  $0^\circ$  were determined by assaying portions of filtrate with mutant No. 1298 after removal of the excess phosphotungstic acid with ammonium ion. The results which are summarized in Table II show that the solubility of cytidine phosphotungstate in 1 N hydrochloric acid is 0.08 mg of cytidine per ml. Cytidylic acid phosphotungstate is soluble to the extent of 0.5 mg as cytidylic acid per ml in 1 N acid but this is decreased to about 0.2 mg per ml in 2 N acid.

The extent to which cytidine could be separated from known cytidine-uridine mixtures and cyti-

dylic acid from known cytidylic acid-uridylic acid mixtures was next determined. The procedure consisted in adding an excess of phosphotungstic acid to the hot 1 N hydrochloric acid solution of an equimolar mixture of the nucleosides or to hot 2 N hydrochloric acid solutions of mixtures of the nucleotides. The solutions were allowed to stand at 0° for from one to three days, and the filtrates were freed from phosphotungstic acid and assayed.

The data which are summarized in Table III show practically quantitative recoveries of uridine and uridylic acid from mixtures of the two nucleosides or nucleotides when the values are corrected

ammonia hydrolysis samples were fractionated with phosphotungstic acid as well and the filtrates assayed for uridine. We have also assayed the acid hydrolysates for adenine (or hypoxanthine or both) with the Neurospora mutant No. 38610 (5) and analyzed for guanine colorimetrically by means of the phenol reagent (4). The results of these several analyses expressed as molar ratios in relation to the phosphorus content of the samples are summarized in Table IV. The values expected from a "statistical" tetranucleotide are also shown.

I shall not attempt to offer an explanation for all

TABLE I  
Analyses and empirical formulas of cytidine and cytidylic acid phosphotungstates\*

SAMPLE	C	H	H <sub>3</sub> PO <sub>4</sub> 12WO <sub>3</sub>	H <sub>2</sub> O
	%	%	%	%
Cytidine phosphotungstate	5.41	1.64	78.7	8.92
Theory for (C <sub>8</sub> H <sub>12</sub> O <sub>5</sub> N <sub>2</sub> ) <sub>2</sub> H <sub>3</sub> PO <sub>4</sub> 12WO <sub>3</sub> 18H <sub>2</sub> O	5.85	1.72	78.2	8.78
Cytidylic acid phosphotungstate	5.46	1.54	78.0	7.2
Theory for (C <sub>8</sub> H <sub>11</sub> O <sub>5</sub> N <sub>2</sub> H <sub>3</sub> PO <sub>3</sub> ) <sub>2</sub> H <sub>3</sub> PO <sub>4</sub> 12WO <sub>3</sub> 15H <sub>2</sub> O	5.65	1.57	78.9	7.1

\* C-H analyses by Laboratory of Microchemistry, 366 Fifth Ave., New York.

TABLE II  
Solubilities of cytidine and cytidylic acid phosphotungstates in hydrochloric acid

EXPERIMENT	1 N HYDROCHLORIC ACID		2 N HYDROCHLORIC ACID
	Cytidine	Cytidylic acid	Cytidylic acid
	mg. per ml	mg. per ml	mg. per ml
1	0.080	0.55	0.18
2	0.084	0.50	0.17
3	0.084	0.50	0.16
4		0.50	
5		0.45	
6		0.50	
Average	0.083	0.51	0.17

for the solubilities of cytidine or cytidylic acid phosphotungstates.

In applying these assay procedures to ribonucleic acid two methods of hydrolysis were used. In the first the sample was heated at 140–150° in the presence of 2.5 per cent ammonia for four hours. All of the phosphorus is liberated as phosphate, and the purine and pyrimidine compounds are presumably present as nucleosides. In the second method the nucleic acid was refluxed with 1 N sulfuric acid for 1 hr., a procedure which converts the purine compounds to free adenine and guanine but leaves the pyrimidine compounds as nucleotides. Both types of hydrolysates were assayed for total pyrimidine nucleosides and nucleotides and after

TABLE III  
Recovery of uridine and uridylic acid from cytidine, uridine and cytidylic acid, uridylic acid mixtures after phosphotungstic acid fractionation

CONCENTRATION OF ORIGINAL MIXTURE PER ML	PYRIMIDINE NUCLEOSIDE OR NUCLEOTIDE ACTIVITY OF SOLUTION ASSAYED AFTER REMOVAL OF CYTIDINE OR CYTIDYLIC ACID (MG. PER ML.)		RECOVERY %
	Found	Calculated*	
0.5 mg. cytidine + 0.5 mg. uridine	0.53	0.47	113
0.5 mg. cytidine + 0.5 mg. uridine	0.51	0.47	108
5 mg. cytidylic acid + 5 mg. uridylic acid	0.23	0.22	105
5 mg. cytidylic acid + 10 mg. uridylic acid	0.435	0.42	104
5 mg. cytidylic acid + 25 mg. uridylic acid	0.43	0.41	105

\* The calculated values include the amounts of cytidine or cytidylic acid expected from the respective solubilities of cytidine and cytidylic acid phosphotungstates.

of the results presented in this table. They have been checked in all cases and are consistent within the limits of accuracy of the procedures employed. There are several significant facts which can be pointed out. It can be seen that the pyrimidine nucleoside content of the nucleic acid samples after ammonia hydrolysis do not differ greatly from each other regardless of their source. The value, however, is about 25 per cent lower than that expected

for a statistical tetranucleotide. While this result may require modification because of possible inhibition by the purine nucleosides as will be presented in the next paper, it is not explained by the decomposition of uridine or cytidine under the conditions of hydrolysis. Control experiments with uridine under similar conditions have shown some destruction but not in amounts sufficient to account for the large difference found. The question of inhibition does not come up for the uridine value or for the total pyrimidine nucleotides. In the first case the inhibiting components have been removed with phosphotungstic acid and in the second case they have been converted to free purines which are not inhibitory. The two samples which were as-

Of great interest is the wide variation in the adenine and guanine contents of the different nucleic acid preparations. These differences were found in different samples of yeast nucleic acid itself as well as between yeast nucleic acid and tobacco mosaic nucleic acid. The two purified yeast nucleic acid preparations represented the portion of commercial yeast nucleic acid precipitated by 5 volumes of glacial acetic acid and that precipitated from the mother liquor of the first by an equal volume of alcohol. The adenine value for the first is about one-half that for guanine, whereas approximately twice as much adenine as guanine was present in the second fraction.

It is also of interest that the uridine values were

TABLE IV

*Pyrimidine nucleosides and nucleotides: adenine and guanine contents of different ribonucleic acid preparations expressed as moles per mole phosphorus\**

SAMPLE	PHOSPHORUS	TOTAL PYRIMIDINE NUCLEOSIDE	URIDINE	TOTAL PYRIMIDINE NUCLEOTIDE	ADENINE (OR HYPO XANTHINE)	GUANINE
	%	M per mol P	M per mol P	M per mol P	M per mol P	M per mol P
Yeast nucleic acid (Lemko 5597)	8.77	0.385	0.21			
Yeast nucleic acid (Schwarz A315 31414)	8.27	0.37	0.20			
Yeast nucleic acid (Schwarz HN 4625)	8.62			0.259	0.59	0.30
Tobacco Mosaic Nucleic acid	8.23	0.363	0.175	0.392	0.60	0.29
Purified yeast nucleic acid (acetic acid insol.)	7.78	0.366	0.179	0.334†	0.16‡	0.31
Purified yeast nucleic acid (acetic acid alcohol insoluble)	8.3				0.53	0.27
Ribonuclease-resistant fraction (acetic acid insoluble)	7.8	<0.016		0.16	0.53	0.49
Ribonuclease-resistant fraction (acetic acid alcohol insoluble)	7.9	<0.016		0.16	0.55	0.31
Statistical tetranucleotide	9.52	0.50	0.25	0.50	0.25	0.25

\* Some of these values were obtained in collaboration with J. McT. Ploeser and Mary E. Buckley.

† Found after hydrolysis for 4 hours with 0.4 N triethylamine.

‡ Calculated as difference between total purine (7) and guanine (4).

sayed for total pyrimidine nucleotides as well as nucleosides gave about the same values by the two methods of hydrolysis.

The results on the ribonuclease-resistant fractions are of interest in this connection. When hydrolyzed with ammonia only a trace of pyrimidine nucleosides can be detected. After ammonia and acid hydrolysis, however, a total pyrimidine nucleoside to phosphorus ratio of 0.16 was found indicating that an appreciable but smaller amount of pyrimidine components remained in this fraction. Analyses of the two resistant fractions for adenine and guanine after acid hydrolysis show high adenine to phosphorus and guanine to phosphorus ratios. These high purine values for these fractions are in agreement with other analyses (7) which indicate that ribonuclease is concerned to a greater extent with the liberation of pyrimidine than purine nucleotides.

approximately one-half those for total pyrimidine nucleoside, although the latter are somewhat in doubt because of possible inhibition.

In conclusion it should be stressed that these results are preliminary in nature and some values will probably require modification as the problem of possible inhibition by the purine constituents is eliminated. The data do provide further evidence that yeast nucleic acid is not a statistical tetranucleotide. We feel that the early work of Osborne and Harris (8) on the ribonucleic acid of wheat germ has provided the only convincing evidence that the composition of a ribonucleic acid may approach closely that of a statistical tetranucleotide. We should like to repeat the statement which has been made a number of times before that ribonucleic acids as usually prepared are not homogeneous substances. In addition to the two fractions from yeast nucleic acid prepared and ana-

lyzed as shown above, further fractionation can no doubt be demonstrated

We should like to offer as a working hypothesis that the composition of a particular ribonucleic acid may not be characteristic of the organism or tissue from which it is isolated but may reflect rather the stage of growth involved. Thus the nucleic acid of an actively growing organism such as yeast might be expected to differ in composition from that present in the wheat seed

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## PURINE AND PYRIMIDINE ANTAGONISM IN THE PYRIMIDINE DEFICIENT *NEUROSPORA* MUTANT, NO 1298

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Among the fractions of hydrolysed nucleic acid examined for pyrimidine activity by the method of bioassay described in the preceding paper (1, 2) was one obtained after hydrolysis of ribonucleic acid with 0.6 N barium hydroxide. This fraction consisted of the hydrolytic products possessing barium salts soluble in slightly alkaline solution. When this fraction was assayed directly with the pyrimidine deficient *Neurospora* mutant, No 1298, only a trace of growth resulted. However, following refluxing with 1N HCl for one hour, the fraction was shown to possess considerable pyrimidine activity. Two explanations suggested themselves, one being that an inhibitor of the mold was present in the nucleic acid hydrolysate and the other that a fragment of the nucleic acid molecule remained which was resistant to alkaline hydrolysis but which produced active components upon acid hydrolysis. The brucine salt prepared from the fraction showed little pyrimidine activity but after nine recrystallizations from 35 per cent alcohol gave a product possessing many times the specific activity of the original fraction. This fact indicated that the original fraction consisted in part of an inhibitor, which could be destroyed by acid hydrolysis. As the barium salts of cytidylic acid and adenylic acid are known to be more soluble than those of uridylic and guanylic acids, it was assumed that the compounds present in the fraction were cytidylic and adenylic acids, and that adenylic acid could be inhibiting the utilization of cytidylic acid. Preliminary experiments showed that this was indeed the case. A systematic investigation of the effect of the various purine

compounds upon the utilization of the pyrimidine nucleosides and nucleotides was therefore undertaken.

The effect of adenine, adenosine and adenosine-3 phosphate (yeast adenylic acid) on the growth activity of cytidine, uridine, cytidylic acid and uridylic acid was determined by adding increasing concentrations of each purine compound to the basal medium supplemented with a constant amount of growth factor. The growth of the mold in the presence of varying amounts of adenine, adenosine and adenosine-3-phosphate was determined and expressed as the percentage of growth obtained in the absence of inhibition. The data for cytidine in the presence of the three purine compounds and for uridine in the presence of adenosine are shown in Figure 1. The amount of cytidine or uridine was 0.5 mg per 25 ml. Of the three purine compounds, adenosine is twice as inhibitory for cytidine as adenosine 3 phosphate. When uridine is used as the growth factor, approximately five times as much adenosine is required to produce the same degree of inhibition. Free adenine fails to inhibit the growth of the mold on cytidine at a concentration equivalent to 0.6 mg of adenosine. Similarly no significant inhibition of uridine in the presence of adenine at a concentration equivalent to 4.0 mg of adenosine was observed.

The inhibition of cytidylic acid and uridylic acid by the adenine compounds was determined in a similar way to that used for the pyrimidine nucleosides, and inhibition curves of the same type were obtained. The molar ratios of antagonist to supplement to give 50 per cent inhibition were calculated for both the pyrimidine nucleosides and nucleotides and are shown in Table 1. It may be

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seen that cytidylic acid is the most readily inhibited, the molar ratio for 50 per cent inhibition with adenosine being 0.13. In contrast to cytidylic acid the ratio for uridylic acid and adenosine was 0.41. It is evident that adenosine 3-phosphate is less inhibitory in all cases than its nucleoside. Cytidine like cytidylic acid is more easily inhibited than uridine, but both pyrimidine

growth is obtained with either cytidine or uridine, it is apparent that the mold can accomplish the amination of uridine or the deamination of cytidine as well as the phosphorylations necessary for the formation of nucleic acid from the nucleosides. Thus when the mold is supplied with cytidine, it not only uses it directly but also to form uridine, and vice versa.

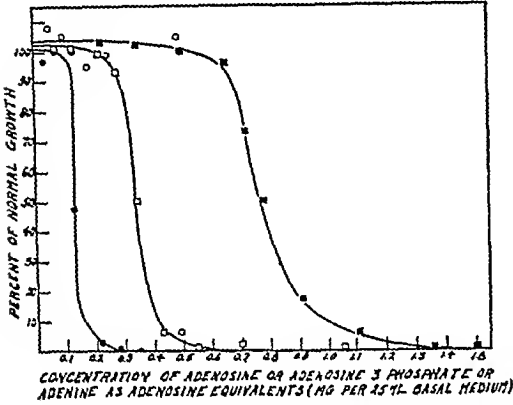


Fig 1 The effect of adenine, adenosine, and adenosine 3-phosphate as adenosine or adenosine equivalents on the growth of *Neurospora* mutant No. 1208, O, adenine, ●, adenosine, □, adenosine-3-phosphate in the presence of 0.5 mg of cytidine, ■, adenosine in the presence of 0.5 mg of uridine

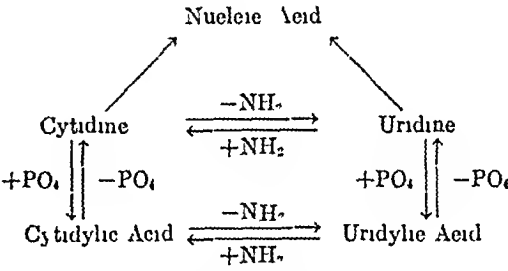


Figure 2 Possible Reactions Occurring in the Utilization of Pyrimidine Ribonucleotides and Ribonucleosides

The surprising difference in the ability of adenosine as an inhibitor of uridine as compared to cytidine suggested that the antagonism is involved to a different degree in these reactions. If the reaction which is inhibited is the deamination of cytidine to uridine, then it should be possible to eliminate the inhibition of cytidine by the addition of enough uridine to avoid the necessity of deamination. An experiment was therefore performed to determine if the addition of uridine would cause removal of the antagonism in a known cytidine adenosine inhibited mixture. The effect of the addition of varying amounts of uridine to a mixture of 0.25 mg of cytidine and 0.27 mg of adenosine in 25 ml of basal medium is shown in Figure 3a, where the weight of mycelium is plotted against total weight of cytidine and uridine used as the supplement. The molar ratio of cytidine to adenosine used was 1.0, which in the absence of uridine produces complete inhibition. The curve showing the growth of the mold on cytidine or uridine in the absence of inhibitor is also presented. It may be seen that the growth promoting properties of the mixtures were almost completely inhibited until an equal amount of uridine had been added. When the ratio of cytidine to uridine reached 1.0, the inhibition had been strikingly eliminated, and as more uridine was added, the amount of growth was approximately that found with either cytidine or uridine in the absence of adenosine. The elimination of the inhibition is a specific one, because as shown in the cytidine-adenosine curve in Figure 1, the addition of another equivalent of cytidine instead of uridine (i.e. 0.5 mg cytidine and 0.27 mg of adenosine) would not have overcome the effect of

TABLE I

Molar ratios of antagonist to supplement for 50 per cent inhibition

SUPPLEMENT	WEIGHT SUPPLEMENT PER 25 ML. OF MEDIUM	ANTAGONIST	MOLS ANTAGONIST MOLS SUPPLEMENT
	mg		
Cytidylic acid	1	Adenylic acid	0.27
Cytidylic acid	1	Adenosine	0.13
Cytidine	0.5	Adenylic acid	0.60
Cytidine	0.5	Adenosine	0.24
Uridylic acid	0.83	Adenylic acid	0.6
Uridylic acid	0.83	Adenosine	0.41
Uridine	0.5	Adenylic acid	3.2
Uridine	0.5	Adenosine	1.4

nucleosides are affected to a lesser degree by adenosine than are the corresponding nucleotides. As the pyrimidine ribonucleosides and ribonucleotides are essential components of ribonucleic acid, it is likely that the failure of growth in their absence is due to a deficiency in ribonucleic acid synthesis. The possible pathways of synthesis are shown in Figure 2. It is unlikely that cytidylic acid or uridylic acid are employed to form nucleic acid directly because of their less efficient utilization for growth. Because normal

the adenosine. Thus it appears that the reaction which is inhibited in this case is the deamination of cytidine to uridine, and that when the mold is provided with an equimolar mixture of cytidine, uridine and adenosine, no inhibition is encountered.

A possible explanation of the effect of adenosine on uridine alone could be the blocking of the reverse reaction, the amination of uridine to cytidine. A larger amount of adenosine would be required for the blocking of this reaction than for the deamination as shown by the larger amounts of adenosine needed to inhibit growth on uridine. If this were the case, one would expect the amount of adenosine which inhibits the utilization of uridine alone to have no effect on an equimolar mixture of uridine and cytidine, both compounds being available for growth. The effect of supple-

with guanylic acid showed it to be less antagonistic towards cytidylic acid than was adenyllic acid, the 50 per cent inhibition ratio being 0.15 as contrasted to 0.27 for adenyllic acid. With 1 mg of diammonium uridyate, no significant inhibition was found when the ratio of guanylic acid to uridylic acid was 1.0.

The striking inhibition produced by the purine compounds on the mutant strain raised the question whether or not a similar effect could be shown with the wild type organism, which is able to synthesize its pyrimidine requirements. Adenosine in an amount of 5 mg per 25 ml of basal medium produced no inhibition.

#### SUMMARY AND CONCLUSIONS

The utilization of the pyrimidine ribonucleosides and ribonucleotides for growth by the pyrimidine deficient mutant of *Neurospora*, No. 1298, can be completely inhibited by the addition of adenosine or adenosine-3-phosphate to the culture medium, with adenosine being the most active antagonist. The free base, adenine, has no antagonistic effect when added in comparable concentrations. The nucleotides are more readily inhibited than the nucleosides which is in agreement with the less efficient utilization of the nucleotides for growth. This result together with the fact that adenosine is more inhibitory than adenosine-3-phosphate and the non-antagonism of adenine leads to the conclusion that the nucleosides may play a more central role in nucleic acid metabolism than either the nucleotides or the free bases.

The blocking of two reactions in the metabolism of the pyrimidine nucleosides is shown by the following. First, a higher concentration level of adenosine is required to inhibit uridine than cytidine, and, secondly, the inhibition of cytidine by an amount of adenosine that will not affect uridine can be entirely eliminated by the addition of an equimolar quantity of uridine. It would appear that one reaction inhibited is the deamination of cytidine to uridine and that the other is the use of uridine itself in the synthesis of nucleic acid. The absence of adenosine inhibition in the wild type organism is in keeping with other observations that no inhibition is produced by structurally related analogues where the substance in question is synthesized by the organism (3).

The demonstration that a balance between the purine and pyrimidine constituents must be maintained for the normal growth of this mutant suggests a similar function for these compounds in the control of growth in other organisms.

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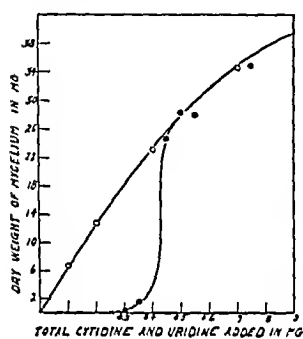


Fig 3a

Fig 3a. The effect of uridine on an inhibited mixture of 0.25 mg of cytidine and 0.27 mg of adenosine in comparison with the normal growth curve for cytidine or uridine. O, normal growth curve on cytidine or uridine, ●, growth curve on cytidine-adenosine mixture with varying amounts of uridine.

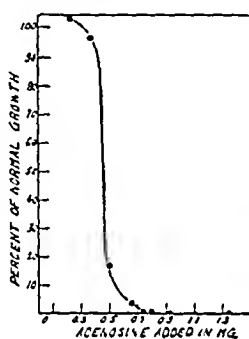


Fig 3b

Fig 3b. The effect of adenosine on an equimolar mixture of 0.25 mg of cytidine and 0.25 mg of uridine.

menting such an equimolar mixture of cytidine and uridine (0.25 mg of each) with increasing amounts of adenosine from 0.23 to 1.4 mg is shown in Figure 3b. The weight of mold expressed as the percentage of growth obtained in the absence of inhibitor is plotted as a function of the added adenosine. When 0.27 mg of adenosine was used, no inhibition occurred, the same result as that given in Figure 2a. However as the concentration of adenosine was increased, mold growth was inhibited in the same manner as that found for uridine and adenosine alone. The molar ratio of adenosine to uridine for 50 per cent inhibition is 1.4, the same as that found when cytidine was absent. The effect of adenosine on uridine is probably concerned, therefore, with the utilization of uridine for growth rather than merely with its conversion to cytidine.

Similar complete studies on guanosine and guanylic acid have been made. A few experiments



# STUDIES ON THE METABOLISM OF ADENINE

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Since the work of Miescher (1) in 1871 with developing salmon sperm, and that of Kossel (2) in 1886 with hens' eggs, it has been known that organisms are able to synthesize the purines necessary for nucleic acid formation. In 1912, Osborne and Mendel (3), using purine low diets, first confirmed this for man. By the feeding of isotopic ammonia, Barnes and Schoenheimer (4), in 1943, showed both in pigeons and in rats, that dietary ammonia nitrogen is rapidly incorporated into the purines and pyrimidines of the nucleic acids of the internal organs. Recently Buchanan, Sonne and Delluva (5), by the use of isotopic carbon, have demonstrated that carbon dioxide, acetic and formic acids, lactic acid and carboxyl labelled glycine are biological precursors of certain portions of the carbon skeleton of uric acid, and, in conjunction with this data, Rittenberg and Shemin (6) have shown that glycine is a specific precursor of a portion of the uric acid molecule. Although the organism is able to synthesize its purines, it would normally be expected that when purines are present in the diet, they would be incorporated into the tissue constituents in an intimate mixture with those otherwise present in the body. The question of the utilization of dietary purines was first investigated by Plentl and Schoenheimer in 1944 (7). They fed isotopically labelled guanine, as well as the labelled pyrimidines, uracil and thymine. They found that there was no incorporation of these compounds into the nucleic acids of pigeons or of rats. The ingested guanine was largely converted to the purine end-product, allantoin, and the pyrimidines were chiefly metabolized to urea and ammonia. These authors concluded that "Neither purines nor pyrimidines supplied in the diet are utilized by the body for the synthesis of nucleoproteins." The unusual behavior of guanine and these two pyrimidines has provoked extensive speculation as to the reasons for the failure of the organism to utilize them for nucleic acid synthesis.

The other purine found in nucleic acids, adenine, is present not only in the nucleic acids, but it also plays a role as a constituent of a number of enzyme systems and in the adenosinetriphosphate of muscle. In addition, adenine and its nucleoside and nucleotides show extensive physiological and pharmacological effects not shown by guanine or

its derivatives. It seemed therefore advisable to investigate possible differences between the metabolic fate of adenine and that of guanine.

Adenine, labelled with an excess of isotopic nitrogen in the pyrimidine ring, was synthesized by the admirable method of Baddiley, Lythgoe and Todd, as shown in the accompanying equations (fig. 1). One nitrogen containing 32 per cent  $N^{15}$  was introduced, resulting in 16 per cent  $N^{15}$  in each of the 1 and 3 nitrogens of the purine ring of the adenine, or 6.4 per cent average  $N^{15}$  content for the molecule (found 6.29 per cent). The sample of adenine used for the feeding experiments was demonstrated to be at least 98 per cent homogeneous when characterized<sup>2</sup> by the counter-current distribution technique of Craig (9).

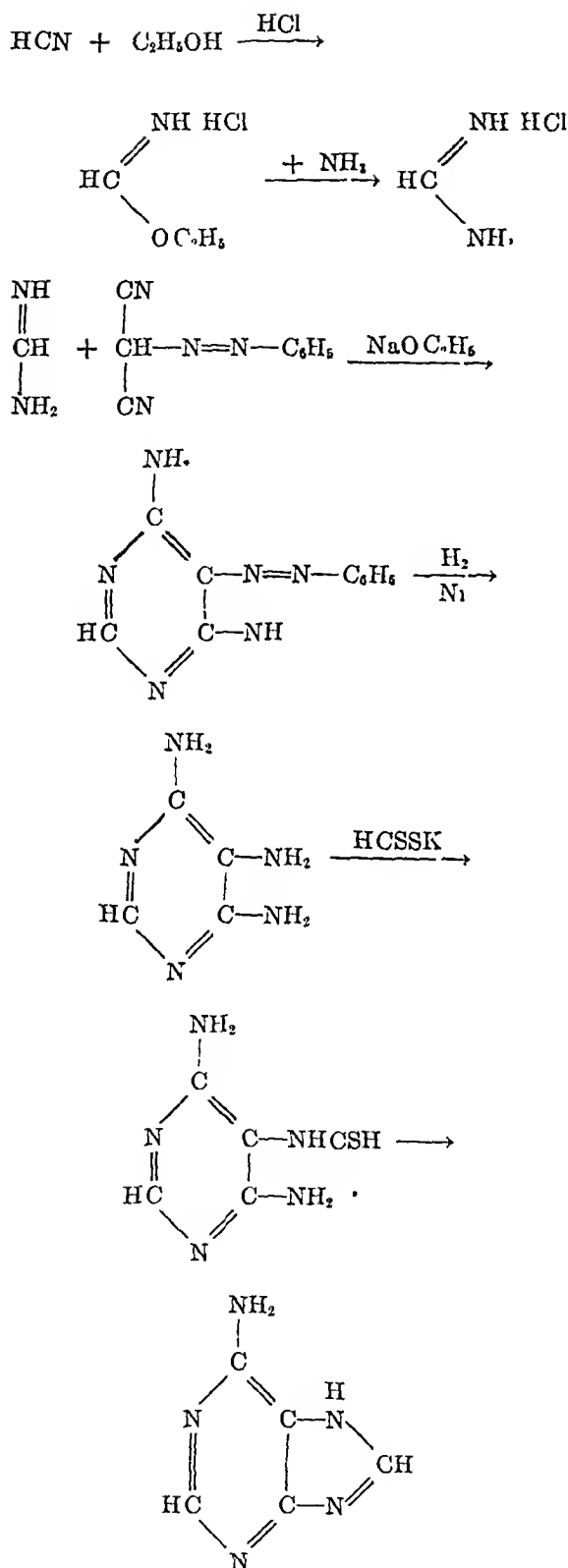
Adenine has long been known to be toxic when administered at high levels. This toxicity, particularly in dogs, has been demonstrated by Raske (10) to produce symptoms of a multiple avitaminosis. To be certain that the amount of the compound administered was not appreciably toxic, preliminary feeding tests were carried out at somewhat higher levels than were subsequently used in experiments with the isotopic compound. Adenine was offered to the rats at a level of 250 mgm per kilogram of body weight per day mixed with Rockland Rat Diet and was fed for a period of six days. The animals ate well without loss of appetite throughout the experimental period and showed no symptoms of toxicity.

In the first feeding experiment with 'labelled' adenine, the adenine was fed at a level of 200 mgm of adenine per kilogram of body weight per day for a period of three days. Five adult, male, Sherman strain rats, of total weight of 1133 grams were fed 680 mgm of adenine over the three day period. They then were fed normal food for a fourth day and were sacrificed.

The sodium nucleic acids were isolated from the dehydrated viscera by sodium chloride extraction. The free nucleic acids were then prepared and these yielded 140 mgm of adenine picrate and 101 mgm of guanine sulfate which were isolated by the method of Levene (11). By counter-current distribution analysis the isolated adenine was shown to be free of guanine and the isolated guanine was shown to be free of adenine. From

<sup>1</sup> The authors gratefully acknowledge the assistance of the Office of Naval Research and the Barker Welfare Foundation.

<sup>2</sup> pH 6.5 phosphate buffer—*n*-butanol, adenine  $K = 2.2$ , guanine,  $K = 0.48$ . J. F. Tinker and G. B. Brown, unpublished data.



Adenine

Figure 1

the nucleic acids the pyrimidines were also isolated as their silver salts

Adenosinetriphosphate was isolated from the freshly frozen leg and back muscles by the method of LePage (12). The three reprecipitated dibarium ATP possessed an N/P ratio of 0.84, which indicated an average of 2.7 moles of P per mole of adenine.

Allantoin was isolated from the pooled urines by a combination and modification of the procedures of Schaffer and Greenbaum (13) and Wiechowski (11). Urea and ammonia were also isolated from the urines.

The isotope content of these isolated products<sup>3</sup> showed that the isotopic nitrogen of the dietary adenine was incorporated into the nucleic acids and it appeared not only in the adenine isolated from the nucleic acids but also in the guanine. A total of 13.7 per cent of the adenine of the nucleic acids was replaced by dietary adenine in the four day period and a total of 8.2 per cent of the guanine nitrogen was derived from the isotopic nitrogen of the dietary adenine during this period.

The pyrimidines contained no isotopic nitrogen, showing that dietary adenine is not a precursor of pyrimidine nitrogen.

The adenosinetriphosphate contained a definite but much lower percentage of isotopic nitrogen. Thus this nucleotide is formed more slowly from dietary adenine. This parallels the observation made by Barnes and Schoenheimer (4) that dietary ammonia is incorporated into pigeon-breast muscle adenylic acid to a smaller extent than into the purines of nucleic acids. It is probable that muscle adenylic acid is not the precursor of the adenylic acid of nucleic acids, although the reverse could be true.

In the case of the urinary allantoin, 27 per cent of its nitrogen was derived from that of dietary adenine. This represents nearly twice as much conversion of the dietary adenine to allantoin as to nucleic acid adenine and probably indicates the existence of a direct pathway for oxidation of adenine to allantoin, a pathway which does not involve its prior incorporation into nucleic acids.

The small amount of isotopic nitrogen in both the ammonia and the urea demonstrates that very little degradation of these purines to either ammonia or urea is involved in their catabolism.

The feeding of adenine at a level of 200 mgm per

<sup>3</sup> The authors wish to express their appreciation to The M. W. Kellogg Company, to Mr. V. H. Dibeler and Dr. F. L. Mohler of the National Bureau of Standards, and to Mr. Steven Friedland of this laboratory for the isotope analyses. The degree of precision possible was not always the same, as a result, some figures are quoted more precisely than others.

kilogram per day is obviously an abnormally high level, so a similar experiment was carried out at a more physiological level. This level of 27 mgm per kilogram of body weight per day amounts to 6.5 mgm per day for a 250 gram rat.

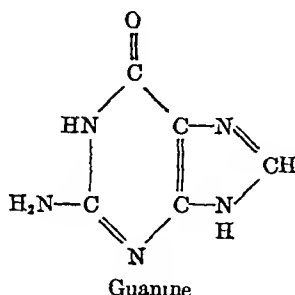
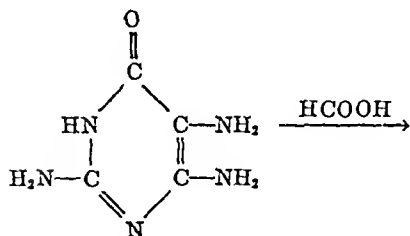
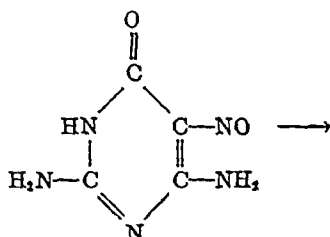
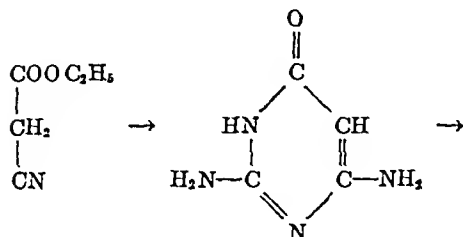
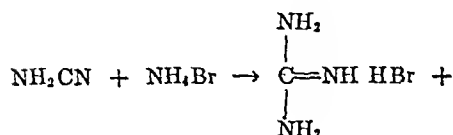


Figure 2

In this second experiment the crude sodium nucleic acids were not analyzed directly, instead, the copper-purines isolated directly from the whole tissues and the mixed purine hydrochlorides

isolated from the nucleic acids were analyzed. In this experiment it was also found that both the adenine and guanine of the nucleic acids were derived from the dietary adenine. They were in the same relative proportion (namely, 1.0 to 0.6) as at the higher level, with the implication that the conversion of adenine to guanine is independent of the amount of replacement of the adenine in the nucleic acids. Although the amount of adenine in the diet in the second experiment was only 13.5 per cent of that in the first, the

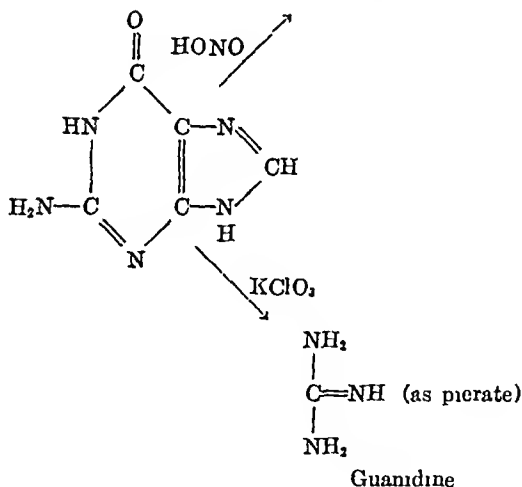
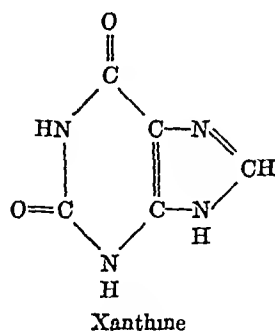


Figure 3

absolute percentage of the isotope in the adenine and in the guanine of the nucleic acids was 39 per cent of that in the first experiment. Thus a more efficient utilization of the dietary adenine for nucleic acid synthesis took place when there was less of it in the diet.

Conversely, the proportion oxidized to allantoin was relatively less. These results are in accord with the fact that the first dosage level amounts to a 'flooding' of the animal with the compound, with a consequent increase in the amount diverted to the degradative route.

In the second experiment, the value for the

isotope content of the A T P of 0.002 per cent excess  $N^{15}$  is of questionable significance for the error on this determination is  $\pm 0.003$ . The turnover of A T P may be extremely slow, and was detected in the first experiment only because the animals were 'flooded' with the adenine.

Because of the striking difference between these results with adenine and the original observations with guanine it was considered advisable to repeat the feeding of guanine with the use of the same diet and the same strain of rats as were used for adenine. The guanine was synthesized<sup>4</sup> by the Traube synthesis previously (7) used (fig. 2). Here the 2-amino group, as well as the 1 and 3 nitrogens of the pyrimidine ring, contain an excess of isotopic nitrogen.

This guanine was then fed under identical conditions and at a level equivalent, on a molar

incorporated into nucleic acids, and that it is extensively oxidized to allantoin. The 'labelled' 2-amino group, which is lost in the oxidation of guanine to allantoin, contributes isotopic ammonia to the body pool which, in turn, gives the urea an appreciable isotope concentration. The ratio between the isotope level in the urea nitrogen and the trace found in the nucleic acid nitrogen is the same as that found by Barnes and Schoenheimer (1) after their feeding experiments with isotopic ammonia.

The difference in the extent of conversion of the two purines to allantoin is more marked when the per cent derived from the purine ring nitrogen is calculated. Almost twice as much of the urinary allantoin is derived from guanine as was derived from the corresponding level of dietary adenine. The extent of conversion to allantoin depends, of

TABLE 1

	ADENINE (200 MG / KG / DAY)		ADENINE (27 MG / KG / DAY)		GUANINE (227 MG / KG / DAY)	
	Atom per cent $N^{15}$ excess	Calcd on basis of 100% in adenine fed	Atom per cent $N^{15}$ excess	Calcd on basis of 100% in adenine fed	Atom per cent $N^{15}$ excess	Calcd on basis of 100% in guanine fed
Adenine (dietary)	6.29	100	6.29	100		
Guanine (dietary)					6.40	100
Sodium nucleic acids	0.356	6.1			0.009	0.14
Copper purines			0.23		0.00	
Purine hydrochlorides			0.23			
Adenine	0.557	13.7	0.34	5.4		
Guanine	0.513	8.2	0.20	3.2		
Silver pyrimidines	0.000	0.0				
Adenosinetriphosphate	0.161	2.6	0.002	0.03		
Allantoin	1.70	27.0	0.348	5.53	2.02	31.6
(Allantoin calcd. as mole % derived from the dietary purine)		(21.6)			-	(37.9)
Ammonia	0.02	0.32				
Urea	0.018	0.29	0.003	0.05	0.115	1.50
Muscle protein			0.00	0.0		

TABLE 2

	ATOM PER CENT $N^{15}$ EXCESS	CALCULATED FOR $N^{15}$ IN POSITIONS 1 AND 3 ONLY
Guanine sulfate	0.513	
Xanthine (from guanine)	0.67	0.64
Guanidine picrate	0.44	
Guanidine	0.88	0.86

basis, to the higher level of adenine which was used in the first experiment. This is 3.4 times the higher level at which guanine was fed by the original investigators (7). The results completely confirm their observations that guanine is not

course, upon absorption and other factors, hence, too much emphasis should not be placed on these figures as representative of the relative extent of oxidation of the two purines.

To begin an investigation of the mechanism of the conversion of adenine to guanine, the determination of the position of the isotopic nitrogen in the guanine which was formed *in vivo* from adenine was undertaken. The guanine was deaminated (fig. 3) to xanthine with the elimination of the 2-amino group. Another sample was oxidized to guanidine, which represents the 1 and 3 nitrogens of the pyrimidine ring as well as the 2-amino group. The results of the isotope analyses on these products (table 2) showed that all of the isotopic nitrogen of the guanine was in each of these products and thus the isotopic nitrogen was still in the 1 and 3 positions of the guanine. Thus the

<sup>4</sup>The synthesis of guanine was performed by Dr. L. F. Cavalieri of this laboratory.

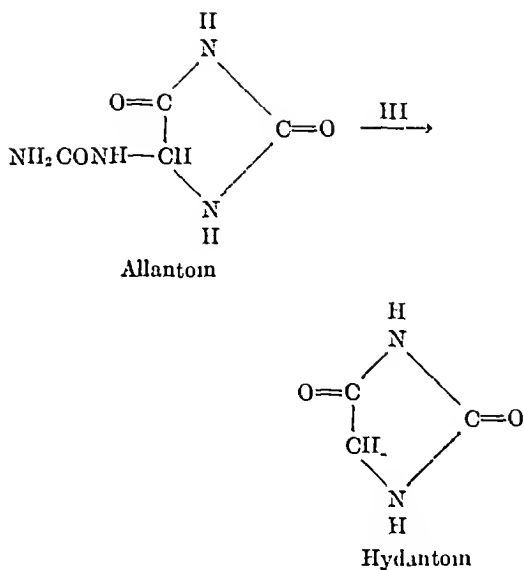


Figure 4

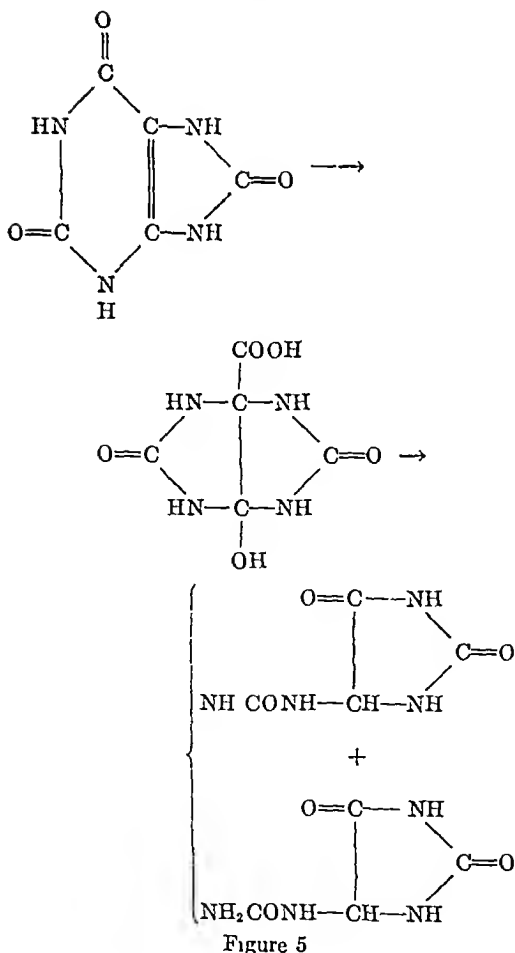


Figure 5

adenine was undoubtedly converted to guanine with the retention of the intact purine skeleton.

The intermediate steps in this conversion of adenine to guanine are yet to be elucidated, but from the data on the feeding of guanine one elimination should be possible now. If xanthine was a product of the *in vivo* oxidation of the isotopic guanine, then xanthine could not have been one of the intermediates in the conversion of adenine to guanine.

The allantoin isolated from the urine after the feeding of adenine was also degraded (fig 4) by reductive splitting with hydriodic acid and the hydantoin isolated was analyzed. The hydantoin nitrogens were found to contain exactly the same percentage of isotopic nitrogen (1.71 atom per cent excess) as the whole allantoin molecule (1.70 atom per cent excess), which indicates a uniform distribution of the isotopic nitrogen between the urea and the imidazole moieties of the allantoin molecule.

There is evidence in the literature to indicate that uric acid, when oxidized *in vitro* reaches allantoin via a symmetrical intermediate (fig 5). Either ring of the intermediate may cleave to produce allantoin with a given pair of nitrogen atoms in either the urea or the hydantoin moieties. Statistically the product isolated will have its isotopic nitrogen uniformly distributed.

By the use of synthetic uric acid<sup>15</sup> containing isotopic nitrogen in positions 1 and 3 this *in vitro* oxidation behavior has been confirmed.

This uric acid has also been fed to rats and it has been shown that the *in vivo* oxidation also yields allantoin with the isotope uniformly distributed. Thus the oxidation of uric acid in the intact animal must also proceed via a symmetrical intermediate.

**Summary** It has been demonstrated that adenine present in the diet is utilized for the synthesis of nucleic acids. The observation of Plentl and Schoenheimer (7) that guanine is not at all utilized for this purpose has been confirmed. In addition, it has been shown that adenine, labelled in the pyrimidine nitrogens, is converted to guanine with the labelled nitrogen still in the same positions in the purine ring. Adenine is the first organic compound demonstrated to be incorporated, as such, into the nucleic acids and provides a tool with which to 'label' specifically the carbon-nitrogen skeleton of nucleic acids.

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## AMERICAN PHYSIOLOGICAL SOCIETY

### REPORT OF THE COMMITTEE ON TEACHING PROBLEMS IN PHYSIOLOGY PERSPECTIVES IN PHYSIOLOGICAL EDUCATION

#### I INTRODUCTION

R W GERARD, *Chairman*

*Department of Physiology, University of Chicago*

Last year a committee of the American Physiological Society reported the results of its admirable survey of physiology in North America. Undertaken at the request of the Council, involving much and able work, presented to a large and interested audience, as a symposium at the Federation meeting, and recorded in the Proceedings (3 407), this venture could not be allowed to end as a reference in some future bibliography. The Council, therefore, last spring appointed a new committee to carry on.<sup>1</sup> Our assignment was, in part, to make an independent judgment on the

status of physiology today and on earlier suggestions for Society action (Supplementary Report of the Survey Committee, July, 1946) and, in part, to explore more fully the education aspects of the larger whole.

It was early decided that further extensive fact-finding was not called for at this time. Rather, it was hoped that adequate consideration of the established facts, by men of breadth but with very different interests, would lead to some unanimous judgments and specific recommendations. Our plan was, then, to meet for several days and to battle through the many dichotomies of opinion to some sort of agreement. Our pleasant experience was that agreement in principle, on all major problems, was present from the start. Most of the discussion was, therefore, at the level of constructive analysis and particular formulation. The committee presents first its analysis of where physiology stands as a discipline, and second its considerations and recommendations for action by the American Physiological Society to further the ends of physiology.

<sup>1</sup> Membership was chosen so as to include, in a widely number of individuals, as wide a range of viewpoints and experiences as possible. It consists of the speakers at this symposium. The committee also profited by the participation, at one or more of its conferences, of Dr K S Cole, W O Fenn, A C Ivy, and M S Visscher. Doctor Fenn, President of the Society, also acted as Chairman during the formal portion of the Symposium. Doctor Gerard led the discussion period following

## II THE PLACE OF PHYSIOLOGY IN THE BIOLOGICAL SCIENCES<sup>1</sup>

PAUL WEISS

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In proper perspective, Physiology appears as an organic part of Biology, one of its strongest, vigorously growing, but still dependent for food and guidance on the common stock, to which, in turn, it renders vital contributions. Our problem of defining Physiology thus becomes simply one of delineation. Just what segment of the great continuum of the biological sciences are we to identify with physiology? The answer varies, depending on whether we follow history, theory, or administrative practice. The three versions do not jibe, and this may be the time to bring them into harmony.

Literally, 'physiologia' means 'knowledge of nature'. Historically, it has come to refer to the dynamic functions of the living organism, in contradistinction to static form and structure. This distinction, however, has collapsed in what might be called the 'analytical revolution' of biological thought through which morphology has just passed. We have discovered that form and structure, far from stable, are in themselves but patterns of activities, no different in kind from the ones encountered in physiological functions. Skin color is but the end product of a pigmentation process, a tissue fiber, the result of molecular alignment, a spindle cell, the product of elongation, any inherited 'character', the last link of a long chain of gene-controlled processes, and so forth. In consequence, we now have the hyphenated brands of Developmental 'Physiology', 'Physiological' Genetics, Histo 'physiology', 'Physiological' Gradients, etc. Sciences that used to rate as morphological, thus give notice that they have adopted the analytical techniques and ways of thinking of physiology and that they, too, aim beyond formal description, at the causal analysis of underlying mechanisms. This has happened, or is happening, throughout biology.

But does it presage a merger into a super physiology of all branches of biology interested in mechanisms of life? There are many signs that such an expansive trend is under way. Unchecked, it would lead to an absurdly watered down concept of 'physiology'. Unheeded, it would leave physiology behind in an absurdly obsolete position. There are voices advocating such a position. This places us in the midst of a dilemma. Which way are we to move?

Let us first examine the expansive trend. Is it really legitimate for physiology to absorb all that deals with 'mechanisms of life'? Or can we draw a logical demarcation line somewhere closer to the old core? I submit that we can, if we define physiology as the study not of 'mechanisms', as is the tendency, but of 'functions', as of old, the term 'function' to be used in the following explicit sense.

All biological systems can ultimately be resolved into populations of molecules. The activities, transformations, and interactions of these molecular groups with the attendant transfers and conversions of energy are the basic instrumentalities of life. They can be measured objectively in units of grams, centimeters, seconds, and so forth, units that contain no reference whatever to the role of the measured events in the household of a living system. We can have complete knowledge of what goes on on the elementary physico-chemical level, without knowing that all of it has a bearing on the maintenance and viability of the organism, and, in fact, makes no sense otherwise. This is strictly analytical procedure. It reveals processes, causal chains of events, facts without meaning in themselves. Yet, what makes life possible, is the very fact that the component processes do make sense, do have meaning, not in themselves, but in terms of the interests of the higher unit. I propose to reserve the term "functions" for processes that have such a referred meaning for the whole, when we are considering them in that relationship.

We can study the operation of a machine without knowing its function. We can likewise analyze physical and chemical processes in the cell without bothering about their functional significance. But if this is as far as we go—and it may be fully far enough for a particular purpose—we need not call it physiology. Let us call it simply biophysics or biochemistry, as the case may be, and speak of physiology only where there is, in addition, search for functional understanding. I say advisedly 'in addition', for, clearly, biochemical and biophysical analysis form the basic tools of physiology. Yet they furnish only part of the story, and what remains is of enough weight to dispel the apprehension that biochemistry and biophysics might soon partition physiology between themselves. The distinction between 'functions' and mere 'processes' should make it easier to decide what to rate as physiology and what not. A cat falling from a roof is an object of physics as long as we are merely interested in the velocity of its

<sup>1</sup> Address delivered at the symposium on "Perspectives in Physiological Education" at the annual meeting of the American Physiological Society in Chicago, May 19, 1947.



fall, or even the acceleration of its endolymph. Physiology enters when we want to know how it always manages to land on its feet. To this extent, physiology marks an attitude rather than a subject matter.

To clarify the relation between physiology and the rest of biology further, we must dwell for a moment on the fact that all biological systems have a dual aspect. They are causal mechanisms as well as products of evolution. Their construction and operation follow universal and immutable laws of physical and chemical causality, just as an automobile is constructed and operated by chains of causally interconnected events, no matter what its style. Of the infinite variety of conceivable forms, however, only a small selection has been actually materialized on this earth. These constitute the existing species and varieties of organisms—of automobiles, and their peculiar patterns are unique and mutable. The causal mechanisms are universally valid and predictable in their operation, the particular configurations in which they are combined to form given types of organisms, however, are historical incidents in a transition of evolutionary styles, and as such, singular, novel and unpredictable. Here is, therefore, a logical borderline. Physiology may want to stay on the side of the repeatable and controllable phenomena and leave the singular and non repetitive course of historic evolution to others.

This is not to de-emphasize the physiological distinctions with which evolution has endowed the various forms. In fact, we never really study respiration or excretion or reproduction as such. We always start from a respiring, excreting, reproducing cat or snail or lobster, or the like. Only secondarily and by abstraction do we derive our generalized concepts. Even then we return again to the specimen to point out how those general functions are specifically fitted to its way of life. But you note that our results will in no way depend on whether this fitness is a product of creation or evolution, or coincidence, for that matter.

This discussion is also pertinent to the recurrent attempts at dividing Physiology neatly into a 'General', a 'Specific', and a 'Comparative' compartment. Such distinctions are expedient for filing purposes, provided we recognize their artificiality. They may become a menace when abused for the purposes of sectarianism. Let me repeat: No function is ever observed primarily in disembodied or 'general' form. We know it only as manifestation of a concrete and specific system. Comparing a variety of such systems, we note common features as well as distinctions. Focusing closely, we recognize specific details, taking distance, details become blurred and general principles emerge in perspective. For the individual, it is a matter of personal predilection how close to the ground he

wants to stick. For science, which aims, beyond mere recording, at insight, it is vital that there be a strong contingent of individuals who are interested in general conclusions and theories. But let us not forget that in any inductive science, such as Physiology, all workers, even those with the most 'general' aspirations, must start from a specific object. It would thus seem indefensible on academic, and most unfortunate on practical, grounds to set off 'general' Physiology as a separate discipline from the 'special' Physiology on which it must draw for its material. The relation between 'general' and 'special' Physiology is as between the stem and the roots of a tree. They can thrive only jointly. Such harmony, of course, requires adjustments from both ends.

We are witnessing increasing strains between the spirit of General Physiology expanding to ever wider orbits, and the practice of Special Physiology contracting to an ever narrower sphere. I have indicated before how to check overexpansion. I am now adding a plea for corrective measures from the other end, to counteract and reverse the excessive contraction on the ground floor of 'Special' Physiology.

Practical considerations force official Physiology into some degree of subservience to professional Medicine. Naturally, man is in the foreground, the nearest mammals are next, and other objects become rather marginal. While acknowledging this development as a practical necessity, we must ask ourselves how far it can go without impairing the progress of Physiology as a whole. In mining, one can go just so far with the intensified exploitation of a narrow strip of land, to persist in mining exhausted low-grade ore, when prospecting in fresh areas might yield pure deposits, does not appeal to the scientific mind. By the same token, it would seem utterly mistaken to overcultivate mammalian physiology to the point where it begins to drain an inordinate amount of attention, manpower, funds, and facilities away from the prospecting activities of a more broadly conceived physiology. Whether this is actually happening or not, you can certainly see signs of apprehension that physiology is drifting into that course.

To realize its hazards, let us just remember, for example, some of the rich returns from past prospecting in invertebrate physiology: the elucidation, in one stroke, of the workings of static sense organs by the ingenious smuggling of magnetic otoliths into the crayfish, the giant nerve fibers of earthworms and squids, the tonic muscles of molluscs, the neuospora assay of biochemical systems, the horseshoe crab model of pacemaker action, the multiple innervation of muscle in crabs, and a host of others. These were strategic break-throughs in an otherwise plodding campaign against the unknown. Innumerable more

such strategic objects are waiting to be spotted and exploited. The physiology of lower forms has scarcely been opened up. Why this lag of Comparative Physiology behind Comparative Anatomy? Presumably for lack of motivation. Comparative Anatomy was sparked by the doctrine of evolution, for which it compiled documents. Comparative Physiology has had no symbol around which to rally. Perhaps, a wider realization and assertion of its far reaching benefits for the advancement of physiology as a whole might do the needed priming. It would also restore better proportions to physiology.

In conclusion, I believe that what physiology needs is pulling its family members closer together, rather than breaking up into clans. If differentiation and social entropy make for disintegration, then our scientific intelligence ought to provide the constructive energy for reintegration.

Well, can this academic blueprint be translated into practical action? After all, we have to recognize that there are certain constraints which economical, administrative, and educational realities place upon our philosophical desiderata. And when we leave lofty theory and come down to the plane of practical affairs, we realize that we are really no longer dealing with the nature of physiology as a science, and what it is or ought to be, but rather with the established connotations of the term in administrative and professional matters, such as departmental structure, teaching curricula, editorial policies, society affairs, fellowships, grants, appointments, and the like. Are we prepared to bring these practical connotations and our concept of physiology into harmony? Let us see what this would imply.

It is evident that Physiology, even in the restricted definition I have advocated, covers a much wider field than do most of the traditional physiological agencies—departments, societies, and journals. It would seem advisable, therefore, that these agencies widen their scope so as to ac-

commodate, rather than obstruct, the new expansion. Yet, we should not expect them to be so over-accommodating as to sacrifice their own identity. Therefore a large area will still be left outside. This marginal area will have to be parcelled up among the nearest border sciences—Zoology, Botany, Bacteriology, Pathology, Psychology, and so on. It will be necessary for these sciences to recognize their responsibility for taking charge of the respective segments, they are not always aware of this responsibility now. For instance, the amount of systematic instruction and research in animal physiology, offered in Departments of Zoology, is still disproportionately small. One of the subsequent speakers will have some more to say on this point.

Such omissions are usually not matters of deliberate policy. Often it is just a case of nobody having pointed them out. Physiology and its border sciences will, therefore, have to get together and find out how many deserving fields they have left out between themselves because each thought they were the other's ward. Undoubtedly, the new American Institute of Biological Sciences could render invaluable assistance in the administrative re-zoning of our biological districts, provided there is the will and spirit on all sides to see the job done. Biology, after a period of groping and dispersion, is recovering its perspective and sense of unity. Physiology, one of its strongest branches, cannot but profit from this trend. Let us, therefore, as physiologists, profess our allegiance to our mother science, Biology, but let us also send a determinate call to our fellow biologists to give physiology its proper share in their scheme. Combining our efforts, we can cope with the problems of an expanding Physiology. We cannot if we keep on fragmenting. Let Physiology and the other life sciences each assert its sovereignty within its own legitimate sphere. But let them, at the same time, wake up to the spirit and the obligations of a One Life Doctrine.

### III THE INTERDEPENDENCE OF PHYSIOLOGY AND MEDICINE

EUGENE M. LANDIS

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From the time of Harvey and Boerhave, physiology and medicine have been linked together historically, scientifically, physically, pedagogically and economically. It is pertinent to ask therefore, "What are (a) the opportunities and (b) the obligations of those physiologists who happen to be located in a medical school?"

The task facing such physiologists is both challenging and complicated. Diagrams are of limited

value but within the limitations of two dimensions, can be used to indicate the central position of physiology when it adjoins both a collegiate and medical environment. As of 30 years ago, one might have drawn (fig. 1) three somewhat amoeboid, overlapping areas with physics, chemistry, mathematics, anatomy and biology at one side blending through physiology to pathological physiology, pharmacology, and then finally to

medicine, surgery and therapeutics. To the right, pathological physiology was from the very first an indeterminate zone between health and earliest disease, a field which is still unexplored in many areas. Recent researches on gerontology, convalescence, early detection of disease, and preventive medicine are cases in point. This is an area in which medical students and clinicians are constantly asking for help both investigative and pedagogic.

Technical and analytic advances have abolished also any clear boundaries to the left because biochemistry, and then biophysics, bridged the zone between physiology and physics or chemistry. It is here that a two dimensional diagram fails to show the manner in which biochemistry and biophysics are now affecting medicine directly. Yet the di-

classical physiology of organs and tissues. This blends in one direction with cellular, general, and comparative physiology, all leaning toward physics, chemistry and biology. At the other end of the scale organismal physiology, ecology and human physiology lean toward pathological physiology and medicine, from which, in fact, many of the truly organismal problems and quantitative studies on man have originated.

This multiplicity of subspecialties is a stimulus, an opportunity and a burden, all at the same time. Clinicians would like the physiologist to be interested to some extent in pathological physiology and disease because as physicians they face at every ward round, and in almost every patient, significant gaps in our fundamental knowledge of function, both cellular and organismal. They transmit these questions to physiologists and find it hard to understand why their immediate clinical problems remain unanswered, while the experienced physiologist attacks them at a fundamental level which seems, for months or years, far removed from the immediately relevant and practical. At the same time the physicists, chemists and cellular biologists shudder at the complexity and the variability of the complicated mammalian organisms with which many of their physiologist friends choose to work.

It is obvious that to expect any one man, or even a reasonably sized group, to encompass all these areas is beyond possibility. Staff, equipment and research problems must be reasonably diverse for a department and yet specialized for the individual physiologist. For most people this is one of the important opportunities offered by a department of physiology in a progressive medical school. It can meet the differing talents and interests of staff and students, if not in itself then by cross connections with sister laboratories in the college, medical school, or hospital. Moreover, it is important to remember that for any one individual neither interest nor talent remains constant throughout a lifetime. Very few physiologists steadfastly continue to work in one specialized research field for one or two decades without change. On seeing a vulnerable spot in an unexplored area of physiology we like to feel free to follow an interesting idea into new methods and materials if necessary. For our research students we like to offer a similar breadth of choice so that productive curiosity may be free and unhampered.

Within this framework, however, specialization in research interests is a foregone necessity with which no one will take exception. Methods, detailed knowledge, insight into the relevant areas of physics, chemistry, mathematics, biology or medicine all force the research worker into a limited investigative field. Moreover, these special interests lead physiologists to enjoy, most of all, their

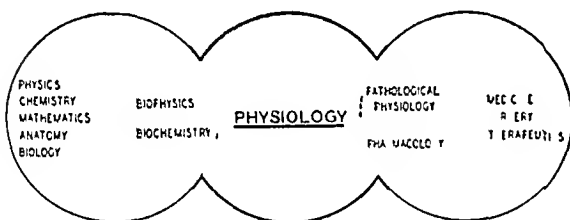


FIG 1

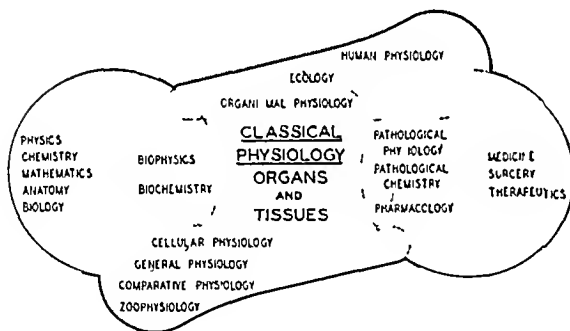


FIG 2

gram is still essentially correct because they influence medicine through the information they provide concerning function, normal or abnormal.

(a) *The trend toward specialization.* One point this simplified diagram completely fails to show, namely the increasing specialization among physiologists themselves, as methods have become more complex and factual knowledge more abundant. It is unfortunate that as physiologists in special fields come to know more and more about less and less, they tend also to know fewer and fewer of their fellow physiologists. It is necessary, therefore, to add at least two other pseudopodia to the amoeba in order to include cellular physiology and human physiology (fig 2). Still remaining squarely in the middle is what may be termed the

teaching and working with, in the laboratory, that smaller number of selected graduate students or research fellows who, like themselves, wish to understand more thoroughly the fundamental principles and methods of physiology for the sake of knowledge and of pure science itself without regard to immediate application. Again, the physiologist in a medical environment can receive and work solely with graduate students, or he can include also young physicians who as research fellows wish to develop their capabilities as clinical investigators and teachers.

(b) *Objectives in the teaching of medical physiology* As to obligations, the most prominent is the teaching of medical students. Physiology occupies with little a central position in the fabric of medical education. The department must receive each year from 40 to 150 young medical students of heterogeneous training and varying interest in pure science. It is expected that these students will absorb in a few months not only the vocabulary of function but also be prepared to deal with the most difficult form of physiology, the study of function in the whole, abnormal human being.

Differences in the students themselves or in their prior schooling make it necessary to scale this instruction so that the brilliant and well trained students will be offered all they can assimilate, while the mediocre or disinterested should at least be taught how to observe, to study, to deal wisely with several simultaneous variables, to use the library, to analyze function judiciously, to record observations, and to interpret them in consecutive and logical fashion.

Therefore, in discussing the training of physiologists, we should really include the training of every student, Ph D or M D, who passes through the laboratory. In this country almost 6,000 medical students are introduced annually to the methods and subject matter of physiology. They are usually selected for their better than average ability, and are committed by their entering medical school to a career which, if not entirely scientific, is in essence a form of physiology to be used in office practice and at the bedside. They are also a potentially influential group some of whom, as leaders in medicine, will determine the future of medical education, medical research and, indeed, of medical physiology itself. Contact with this group is our heaviest annual burden, because of the number involved, but it is still an important opportunity. Despite the unfortunate economic differences between the vocations of medical practice and pre-clinical research and teaching, one may ask whether the failure to attract more of our abler medical students into physiology may be partly due to our offering something less than the best possible teaching to the best of the class either because of limited budgets, or because

the annual course is something to be got through with as quickly, cheaply, and easily as possible.

(c) *Stimulation of young physiologists* At this point it is helpful to consider some of the influences which have apparently led men of our own generation to seek training in physiology. Dr S S Visser of Indiana University has recently collected 'background information' on those scientists whose names in American Men of Science have been given a star to indicate outstanding scientific contributions in their respective fields. With gratitude to Doctor Visser for the privilege, I can present a summary of the motivation, stimulation and training of 48 physiologists whose names have, by vote of their contemporaries, been thus starred in one or more editions of American Men of Science between 1903 and 1913. With all necessary reservations concerning conclusions based upon even the

TABLE 1  
*Training and motivation of physiologists\**

	RELATIVES AND FRIENDS	HIGH SCHOOL TEACHERS	COLLEGE TEACHERS	GRADUATE TEACHERS INCLUDING PHYSIOLOGISTS OF MEDICAL SCHOOLS	OTHERS
	percent	percent	percent	percent	percent
Decision to enter science attributed to					
Stimulation to high achievement attributed to	38	18	41		3
Major contributions to later achievement attributed to	32	4	31	31	2
		10	28	61	1

\* With gratitude to Dr S S Visser who kindly permitted my summarizing questionnaires submitted by 48 physiologists in a larger canvass of 'starred scientists'.

best of questionnaires, the results are interesting because they put physiologists in medical schools, so to speak, in their place and also on their mettle.

These 48 prominent physiologists decided to follow science as a career at the median age of 18, half of them between 17 and 20, and a fourth between 7 and 16, only 3 came to this decision when older than 22. They decided to make physiology their career at the median age of 22, with variations between 9 and 40, but with more than half of them at age 20 to 23. As shown in table 1 the decision to enter science was attributed to the influence of college teachers by 41 percent, to relatives and friends by 38 percent, to high school teachers by 18 percent, and to no outside source by 3 percent.

Credit for stimulation to high achievement was assigned somewhat differently, to relatives and

friends by 32 percent, to college teachers by 31 percent, to postgraduate teachers including medical by 31 percent, to pre college teachers by 1 percent, and to co-workers by 2 percent. Hence the initial stimulation of young physiologists in the 4 decades past seems to have come chiefly from relatives and college teachers. The minds and personalities with which graduate and medical schools work, appear to be selected during their earlier and more formative years, in the home, high school, and college.

In contrast, when major *contributions* to later achievement are considered graduate work and postdoctoral study lead with 61 percent, college work comes next with 28 percent, precollege work with 10 percent, and no outside contribution, 1 percent. Those who gave the names of exceptionally helpful preceptors chose, in the vast majority of instances, well known men working in the physiology departments of medical schools here and abroad.

If we wish to consider ways to obtain a better selection, or a greater number, of young physiologists, we must admit that our present influence is not as important as it might be. It appears that we have been indebted to parents, friends, high school teachers, and college teachers for the major number of candidates. This is mentioned not as an invitation to lobbying but as evidence that those of us who are located in medical schools should consider the long range implications of a too narrow concentration on the purely technical aspects of our branch of learning, to the neglect of encouraging teachers of physiology in secondary schools and colleges. This is particularly true now when the social implications of pyramiding technical, but unoriented, knowledge are being scrutinized critically by those scientists and non-scientists who are interested in a stable and cooperative understanding of the true aims and value of the scientific method in modern life. For example, Howard Mumford Jones in his essays *Education and World Tragedy*, deplores the increasing tendency to train scientists predominantly as superb research technicians in a narrow field, to the neglect of their broader development as carriers of a flame in a philosophic and pedagogic sense. In physiology particularly, specialization and emphasis on technology must be balanced by recognizing the value of some general philosophy within the science. Otherwise we may soon lack in this country the personalities and schools of physiology which are needed to continue the traditions of Lusk, Mendel, Howell, Cannon and Carlson.

Similar criticisms have been levelled against medical education and its specialties. For example, clinical teachers and various examining boards have complained repeatedly that students, interns, residents, and even specially trained physi-

cians tend to neglect the observational and physiologic approach to clinical problems, becoming thereby unduly dependent on 'rules of thumb', instruments, laboratory analyses, and special tests. While physiology is only one of the pre clinical sciences, we should assume special responsibility in medical education for starting proper habits in careful observation, wise experimentation, accurate recording, and judicious interpretation of interlocking functions. In the physiology laboratories, for the first time in their long education, medical students can logically be faced with the intricate responses of the whole human being, just as our graduate students, in aspiring to the Ph.D. degree, are quite appropriately expected to concentrate their reading and laboratory work on the advanced investigation of single functions. Both approaches present interest and specialized appeal because of direct relevance to the respective aims and ambitions of these two groups of students.

For graduate students it is important and profitable to encourage their interest in some aspects of physics and chemistry because they are necessary for fundamental research in physiology. For medical students it is equally important to make full use of the techniques by which normal function has been studied quantitatively in man particularly during the last two decades.

(d) *Stimulation of medical students.* Medical students cannot escape their conditioned feeling that man is for them the most important animal. To begin the very first laboratory hours of a course in medical physiology with a general orienting study of certain gross and easily measurable responses of the normal human being, is not only logical but also stimulates an immediate interest in function because of its obvious relevance to their future vocation. Guided by appropriate laboratory instructions they can discover the meaning for man specifically, of important general concepts such as 'the normal state', 'control period', and 'reaction to stress'. Moreover, in many respects we can define the normal range of variation of a given function and its quantitative reactions to stress more accurately and easily in the human being than in the common laboratory animals. These future physicians, and we may add, future physiologists, learn at once, with a minimum of unfamiliar apparatus and a maximum of direct, semi quantitative observation, that carefully planned, well controlled and systematically recorded studies on man can be revealing up to a point and then become highly perplexing. They find that the answers obtained merely give rise to still more questions, and from these they appreciate the necessity for the analytic and controlled experiments of pure physiology.

The perplexity that this abrupt introduction

produces dare not, of course, be overdone lest a superficial 'practical' attitude be developed. As a brief introduction, two to four days' work on man is a useful and stimulating experience for students very few of whom have ever before been required to think in terms of many variables. It has been interesting to observe that the more thoughtful students discover at once for themselves the value and intellectual satisfaction of analytic studies on simpler preparations such as the heart of the turtle, or the muscle, nerve, and capillaries of the frog, or the smooth muscle of the rabbit's intestine. Even the less thoughtful students, often blasé and impatiently skeptical of physiology's usefulness to them, are more apt to become interested when they are confronted first of all with some of the perplexing and interlocking reactions of the intact human being.

When observations on isolated tissues are presented first, and without prior experience with the whole organism, some students tend to regard them as delaying, technical exercises which have no discernible relation to the human being, normal or abnormal. Yet, when introduced somewhat later after a more general view of the problem, these same exercises are welcome. They then demonstrate the rôle that 'pure' physiology plays in medicine. Just as physiologists and physicians were forced to do in the past, so the student can again, and for himself, profitably recapitulate in the laboratory a few of the questions and experiments which have required the development of physiology as a 'pure' science.

Students should end their course in medical physiology with the distinct feeling that they have barely scratched the surface and that, for some of them, physiology has important contributions to offer either as training for research or as a life work. Fortunately, student research fellowships are now available to encourage advanced research training in a pre-clinical science for a period of one year. This year may be interpolated between the second and third, or between the third and fourth years of medicine. Encouraging the abler, interested students to drop out of their set course in medicine for a year of research training will make better physiologists of them whether they use its principles in the teaching and practice of medicine or in the teaching of physiology. In coming years the number of applications for these 'Student Fellowships' may well serve as a valid measure of the interest aroused by physiologists in their respective medical schools.

(e) *Exposition of factual physiology for biologists, medical students and physicians.* Finally, we may ask whether the fundamental principles and the detailed facts of physiology can be presented more helpfully than at present. The increasing mass of detail has forced publishers to change most

of our text books from single authorship to a series of brief monographs collected in one limited volume. Each writer must preserve an uneasy balance between the proved and speculative, as well as between the fundamental and practical. Excellent compromises though they are, these single volumes necessarily provide abbreviated discussions of general principles and include very few illustrative examples of integrated functions because of the details they are also expected to include. To this extent they fall short as a stimulating introduction or guide to an important science. On the other hand, they cannot do complete justice to newer literature and conflicting opinion, nor can they provide references to all the original papers that would be helpful to the biologist or the physician who wants all the facts to aid his own research. To that extent they do not offer in collected form the best that physiology has to offer as a science.

Once this dilemma is generally admitted, it might seem desirable to meet these two separate needs more satisfactorily by two very different but closely interlocking types of exposition. For instance, it might be an interesting experiment to prepare for medical students a smaller volume, which is not a compendium or synopsis, and not merely superficial, but is by design limited in scope. In such an introductory volume exposition might progress from a statement of the general problems of organismal function, with particular reference to man, and from that to the general principles involved and then to specific functions and their analysis. In the end the subject matter would be, as always, normal analytical physiology. The chief difference would be one of arrangement. Such a volume prepared for medical students should approach the subject of function generally in the manner that physicians are forced to use in the orderly observation, analysis and diagnosis of abnormal function in the intact human being. A similar introductory volume prepared for biologists should be oriented quite differently to stress the comparative aspects of special functions.

Of highest importance would be the avoidance in such introductory volumes of any hint of dogmatism or superficiality. The introduction to physiology should be made practically continuous by means of many cross references with a companion and larger volume, or better still a set of 2 or 3 frankly monographic, loose-leaf volumes. In the latter, general background being assumed, collected sections prepared by specialists could be written at the graduate and research level with all the reservations and bibliography that are required for scholarly descriptions of current problems. The interest and questions stimulated by the introductory volume should naturally lead students to the larger volumes and thence to the

original literature. Such a series of renewable, up to date volumes would also make more available to clinicians the results of research by physiologists. Physicians want and need this fundamental, factual information which physiologists themselves are most fitted by experience to provide.

To summarize, the numerous opportunities and obligations facing physiologists who follow their science in medical schools lead one to hope that the training of young physiologists may always be individually fitted to their special interests and talents in a broad field of biology. Little is gained, and much may be lost, by forcing intellectual activity into any exclusive and unyielding mold.

For the man who enters physiology after completing medical school additional training in biology, cellular physiology, advanced chemistry and physics is essential. For the man who enters physiology direct from college, familiarity with the quantitative aspects of human physiology will

provide him with a broader concept of all biology. One should not say that a physiologist must always be a Ph.D. or an M.D., or both, but rather that a department is apt to be better balanced if both viewpoints can be represented adequately and with mutual understanding.

Finally, in a science which prides itself on its experimental method it would be wise to include cautious experimentation in the stimulation and training of physiologists in all areas,—collegiate, graduate and medical. In that respect we are fortunate because we are dealing with a subject which is old enough in years and experience to appreciate its strength and weaknesses. In problems and facts, pure and applied, physiology is still immature enough to provide frontiers for research which are both wide and deep. It is an area which can and should utilize the widest possible variety of methods and talents both in research and in pedagogy.

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#### IV EDUCATION FOR THE BROAD ASPECTS OF PHYSIOLOGY

LAURENCE IRVING

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In considering education for physiology we should first determine what sort of a world we live in, and if education does not fit the times we should direct our efforts toward attainable improvements.

After World War I citizens of the United States made such rapid progress in improving standards of living that in 1939 it seemed likely that they need never again be exposed to the physiological stresses of hunger, thirst, cold, wet and heat, except through folly or mismanagement. Suddenly in 1940 millions of citizens began to join with millions from other nations in facing exposure to tropical, desert and arctic climates at ground and sea levels, at high altitudes and under the seas. The speed and volume of transportation often moved men into physiologically unbearable situations faster than even a small degree of physiological acclimatization could be established. Strategic considerations placed men in physiologically dangerous areas before knowledge and protection could prepare for their safety. Great numbers of men from civilized regions sought to use complex modern machinery in rigorous environments where previously many generations of people had barely established a precarious existence.

During the early part of the war military success came from the surprising hardihood of men in enduring physiological vicissitudes beyond the limits expected of human tolerance. Spiritual forces undoubtedly extended their physiological ability and

brought about accomplishments above those of common endurance, but our enemies appeared to be impelled by forces of equal strength.

Now the strategic lines of war are maintained for peaceful observation and communication. While military forces are less numerous, the numbers in physiologically strange situations are still large, and to them have been added many civilian administrators and observers. They are stationed in all environments,—tropical, desert and arctic, aerial, marine and submarine, for political, commercial, scientific and technical observation and for the maintenance of communications which we hope will establish peaceful intercourse throughout the world.

Most of the peoples with whom we would like to deal are not so fortunate as we. Not half of the world's population has food physiologically adequate for activity at a rate significantly above survival. Already weak from hunger and exposure, many peoples are so ravaged by parasites and disease that there is no reasonable hope that unaided they can become comfortable or an asset to the community of nations.

In such a world much of human misery is definable in physiological terms, and the remedies available can only be assessed and applied on the basis of physiological estimates. There are too many peoples whom we do not know sufficiently well to be able to work with them in harmony. Part



of the objective assessment of each nation's capability for good or evil rests upon the way in which we understand the balance between their national existence and their environment in physiological terms

Throughout the world important natural resources are located in areas physiologically unsuited for our present means of living and working. Through such difficult areas pass important lines of communication, and there it is necessary for cultural and practical reasons to establish outposts for scientific observation and research.

A new set of physiological stresses has come upon civilized man in his application of power through mechanisms of a new technical order, and men now work with power, velocities, frequencies and radiations of new and still unknown physiological influence.

Recognizing that barriers of physiological ignorance hinder our communications and observations in a large part of the world, the Joint Research and Development Board has established a Panel on Expeditionary Physiology in the Committee on Geographical Exploration. This Panel developed from the deliberations of a Committee of the National Research Council on Field Research in Comparative Physiology. I have thus been able to see that organized and purposive deliberations are considering means for new applications of physiology to the better understanding of the world.

It is not being overcritical to suggest that our system of education was not designed for present conditions. Nor is it being too ambitious for physiologists to suggest that by broadening physiological education the prospects for meeting new world conditions widely can be significantly improved. In making this suggestion before, I have received the answer that education is too busy with basic routine and with established forms to permit extending physiological training over such broad fields as I have outlined. Neither is life so long that any individual can afford to spend more time in school. But there are many schools, our system of freedom permits wide ranges of curricula and the education of a physiologist continues over many years. So it is not my thought that undergraduate and graduate institutions alone can completely survey the new world during a few years' instruction of youth, nor that formal education should be prolonged. Nevertheless, if the academic system is to remain the basis for education, it should provide basic education in physiology which will enable physiologists to survey the environments in which people are already living and to cross the many frontiers which are now being scientifically explored.

In academic usage Physiology has come to mean the small part of the subject which is covered in

faculties of medicine, and as a consequence each new growth takes a new name and departs, taking the scene away under this new designation, a procedure which suits academic housekeeping but breaks up the one profession which is concerned with the operation of life. It has been suggested that Zoophysiology could be used to reassemble the broad considerations for life which Physiology has given up. The term Zoophysiology shows that physiological interest is directed toward the life of animals. It is broader than 'descriptive' or 'comparative' physiology. It includes that part of General Physiology which applies to animals and human's and it is distinct from Medical Physiology. The value of the designation has been demonstrated by the work of the famous and unique Laboratory of Zoophysiology in Copenhagen.

For illustration of the first division of Zoophysiology which needs emphasis, I will name the following subjects,—lactation, hibernation, flight of birds and insects, respiration of diving mammals, migration of animals, conversion of energy and substance in animals and the genetic segregation of biochemical reactions. These views of the subject could be classified under Zoophysiology as Descriptive Physiology, although I fear that many will be prejudiced by the simplicity implied.

The subjects above could be considered as Comparative Physiology, but I think that they are really of general biological and physiological concern, and I would save the designation Comparative Physiology for well organized physiological information about series of animals arranged with regard for phylogenetic relationship. There is much value in such comparative views when applied to respiratory mechanisms, renal secretion and certain nervous and sensory functions. In regard to many functions, however, physiological descriptions have not accurately covered a sufficient number of forms to give such sequences as have enabled comparative anatomy to establish broad biological generalizations. There is every reason to anticipate that through systematic pursuit of Comparative Physiology new and important generalizations will begin to appear.

Especially timely is the study of the relation between physiological events and the natural environmental conditions which call them into view. Examples of subjects in Environmental Physiology would be acclimatization to heat, cold and altitude, the tolerance of desiccation, heat and cold, and the physiological relations of animals to the saline substances of soils and natural waters. It was impressive during the war to see it emphasized that human life is physiologically suited to limited environmental conditions which prevail over only small areas on the earth. Beyond these frontiers men can, however, survive by knowledge, training

and equipment, and there still remain interesting areas of earth, sea and atmosphere which could be explored if physiological knowledge were sufficient. Rapid progress has been made in mapping the world in terms of climatic and other physical and chemical factors of the environment. With the speed and volume of travel the opportunities for observation are numerous and the obvious dependence of animal activity upon environmental physiological relationships makes this subject of timely interest and importance.

New applications of forces and power have produced velocities, frequencies and radiations of still unexplored physiological influence, and from now on the life of animals and of man will be exposed to new types of man-made environmental factors which present important practical problems and raise many clear questions of basic physiological interest.

I do not know whether General Physiology or Zoophysiology is the broader term. Under General Physiology have fallen many important studies aimed toward the definition of physiology in terms of physics and chemistry. I doubt if these sciences are at present sufficient for the description of biological phenomena, but the advances in General Physiology need not be retarded to debate its limitations until much further progress has been made.

I have not listed Medical Physiology as a branch of Zoophysiology for the simple reason that organized physiology has developed as a function of medical education, practice and research. It suffices to illustrate this statement that out of the first twenty-six names in the Federation list for 1946 twenty were employed in institutions of medicine. In surveying the list of past officers I did not find any names not associated with medicine. As one of the few physiologists not concerned with medical subjects I wish to make grateful acknowledgment of the help and scholarly companionship which I have received from my colleagues in medical institutions, and I am deeply impressed by the liberality which medical education and science show. Only praise is due to medical science for bringing about the development of physiology, and it is inevitable that the scientific institutions of medicine should dominate the physiological society and profession, for outside of the institutions of medicine there is but little support for physiology.

Medical institutions have been responsible for the development of physiology, and no other institutions in this country offer to take up that responsibility. Apart from medicine, there are few posts and laboratories primarily for the study of physiology. While the physiological subjects which I have mentioned under Zoophysiology are interesting to medical physiologists, there seems to

be no basic reason for placing responsibility for physiological studies of such broad importance upon a single profession. With mounting costs of medical care coming under critical review only bad accounting practice would expect medicine to be charged with the cost of so large a section of scientific education as is included in Zoophysiology.

There have come up occasional groups and even a few institutes for the study of Human Physiology in industry, sports, climatic tolerances,—in short, the common and extreme activities of normal men. But the careers open in these important and interesting fields, which are so different from those in Medical Physiology, do not give encouragement to the student who is seeking a profession.

In what institutions other than medical may we look for the development of physiology and physiologists? The largest educational institutions concerned with biology are to be found in the schools of agriculture, wherein pure and applied science flourish principally under State support. Here there is a great diversity of scientific and practical interests. While the physiology in these institutions is of the greatest importance it is not organized as a basic science as is physiology in medicine.

Primary consideration for its application rather than for its basic value makes physiology important in such other institutions and departments as entomology, public health, pharmaceutical production, forestry and conservation. Because of special economic values we can look for physiological research and education to increase rapidly in these institutions, but we probably will not find the degree of purity in support of the physiological profession that has developed in medicine.

Museums of zoology and natural history and the zoological and botanical gardens have been the bases for most of biology with the exception of physiology. In spite of occasional direct contributions to comparative physiology, animal behavior and environmental physiology from the museums, physiologists have made little use of these ancient and strong foundations of biology. Through the museums and zoos physiologists could find many new vistas of research and education in pure and applied physiology. In the museums and zoos exist the collections of animals and biological information basic for studies of the physiology of animals, including man, in natural environments throughout the world. If that definition seems too broad, I would suggest that you take an afternoon to look at the collections in the nearest zoo and museum of natural history as naturalists, while thinking about them as physiologists. Consider the great expansion of your knowledge which might come if you could pick the best animals of the world for physiological research rather than the few poor

species which accept the restrictive environments of domestication. If you consider the various natural backgrounds of the whole list of animals you will see how the museums and zoos could help you and your students to prepare for field studies of life in environments established by natural influences rather than by the arbitrary acts of man.

Over another great source of new and progressive physiological knowledge most of us are drawing the curtain as we try to eradicate the influence of our experience in war. I have no patience with those who complain that science did not progress during the war. About fifteen million citizens of the United States alone had experience in environments completely new to them. Many have returned to our schools with greatly improved ability to receive education. In viewing the scholastic performance of veterans it seems that the last few years were better spent by a young man at war than at school. Most of our young men did not experience combat, and it is evidently not the "horrors of war" which account for the improved educability of veterans. It might be that absence from school permitted the development of important steps in the maturity of youth. But the men returning to school are varied in age and the young seem to have matured while the older ones have a refreshed youthful sincerity in their view of education.

The experience of men in new climatic and social environments, in the operation and care of air craft, submarines, communications and all of these new devices over which youthful soldiers have exerted such amazingly skilful control has given to young men a new confidence in their ability to observe and act. It has impressed upon them the value of accuracy and the peril of mistakes. The world has suddenly become more interesting, the power of human action has increased, and among the young at least there is a new appreciation of the possibilities for the enjoyment of collaborative work and life.

I have made no statement that war, or a military

system, is good. But it happens that we still carry on our international work through a large military establishment and there is no substitute in view. This establishment employs many men and moves them to stations in all climates for work among many people. In military work are employed the modern instruments which by their power and precision present unique physiological experimental opportunities. Here are chances, or rather requirements, for physiologists to explore all lands and environments, with their animal and human populations, and to experience the physiological effects caused by civilization's newest instruments.

Physiologists now face a period with fantastic opportunities for scientific experience. And they face a prospect in world affairs in which miscalculations of the physiological bases of life imperil the existence of individuals, nations and of civilization.

To prepare for these functions the education of physiologists should take a large view and energetic action. There is need for educational institutions in physiology more elementary, more nearly basic and much broader in scope than those now provided by medicine. I suggest that institutions and departments are particularly needed for descriptive physiology and for studies preparing physiologists to investigate the life of all animals in the field in all environments and conditions. The facilities for broadening physiological training are largely waiting unused by physiologists in institutions for natural history and in the military establishments. Their employment for physiological exploration upon a scale of world wide interest and usefulness requires ventures outside of the laboratory and promises intellectual adventure upon exciting frontiers of physiology. The exciting prospects on these frontiers could become a lasting incentive for vigorous young men which might carry over permanently to education the vital stimulation which has been observed so often in the past to follow briefly after the intensified activity of war.

## V THE TASK OF THE AMERICAN PHYSIOLOGICAL SOCIETY

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The preceding papers have presented vividly several facets of physiology. Our subject emerges as potentially the trunk of biological science, rooting into fundamentals of physical science, branching into all biology, and leading into a wealth of applications in clinic, farm, factory and government. In actuality, it is rather less than this, although the functional or dynamic approach is, indeed, sweeping ahead in all areas of biology. Physiology is what physiologists do in their professional capacity, and physiologists are the men appointed in physiology departments, accepted in the American Physiological Society, awarded degrees in physiology, and the like. Since academic physiologists determine the training of recipients of degrees and dominate the American Physiological Society, their attitudes and actions essentially define physiology.

These men, in turn, are chosen by administrators who may or may not have some over-all conviction of what physiology should be or become, and who may or may not seek widely for judgments of this sort. Further, the bending of inherited departmental lines, inevitable local accidents, and the march of knowledge, continuously blur the simple assumption, above, that departmental affiliations define a field. Indeed, the question of how much biology and medicine should be subsumed in a department of physiology or how much of physiology should be incorporated into other departments may become mainly an administrative or jurisdictional one.

If, therefore, the future development of physiology as a science is to receive any thoughtful direction, this must come from the American Physiological Society—the acknowledged organ of American physiologists. By its decisions as to membership, by the character of its activities, by any official positions it takes, the American Physiological Society exercises a profound influence on the course of physiology. This is an opportunity and a responsibility and should be faced with open eyes and minds, for inaction or casual action, no less than well-planned action, has far-reaching consequences.

Historically, the American Physiological Society has been concerned overwhelmingly with research alone. It has not concerned itself with educational matters in physiology, with economic problems of the profession, with relations to other biological or broader scientific groups (except for the Federation itself and the International Congresses), or with the wide community of which it is a part. Even in the research area, its scope has

been kept limited. These limitations have caused many workers to feel unwelcome in the American Physiological Society, even as investigators, and many more to feel their interests incompletely represented in it, and have resulted in the formation of more or less formal schismatic groups of various sorts.

It may be helpful to introduce here some of the pertinent findings from the questionnaire study made by the former committee. About two thirds of professed physiologists have the Ph.D. and about one third the M.D. degree (Dow), the entry of M.D.'s into this profession centered on the year 1926, of physiology Ph.D.'s on the year 1936 (other Ph.D.'s, 1930), and, today, few men possessing only an M.D. degree remain actively in physiology (Boyd). Until the war, about 75 Ph.D.'s were hatched a year in North America, some 10 percent of all the Ph.D.'s in biology. Many of these men have been assimilated into other fields, while somewhat fewer men with Ph.D.'s in other disciplines have been absorbed into physiology. Only half of the present population of professional physiologists obtained the Ph.D. degree in physiology, and hardly 40 percent of the members of the American Physiological Society have academic positions as physiologists.

Your present committee (and consultants) met last spring and fall and considered the status of physiology in relation to the American Physiology Society. It came to unanimous opinions which, it later appeared, were also in accord with those of the previous committee. The problem was outlined in May 1946, for this committee, in part, as follows:

The central question around which all the turmoil about physiology education revolves is the simple one, "What is physiology?" There have been two opposing tendencies, one to make it a vocational or service field, concerned primarily with the training of physicians and with research closely related to medical problems, and the other, a liberal or general discipline tending to tie in with the rest of biology. This can be paraphrased in several ways for emphasis. Vocational versus liberal is represented strongly in the debate as to whether the degree needed by physiologists should be the Ph.D. or M.D. It involves the argument as to training, whether physiologists should spend time in physics, mathematics and chemistry, or pharmacology, pathology, anatomy and some clinical experience. It involves the respective emphases in physiology departments themselves on what may be called 'theoretical physiology' versus 'human physiology' or 'applied physiology'. It involves, finally, the ultimate question of whether a physiology department should be centered on a medical contact or on a biological con-

taet or both, or some one and some the other, whether the core of the teaching should be a course for medical students with some 'general' physiology thrown in as a special requirement, or whether the core teaching in the department should be basically biological with special courses in human physiology thrown in for the medical students, or whether no core is possible, and whether physiology is to remain or become the central biological subject about which are built, is specialties, biophysics, general physiology, physiological zoology, physiological psychology, physiological bacteriology, physiological anatomy, physiological botany, and whatever else you want, or whether the center of gravity of biology is to shift to or remain in some other area, such as zoology or biophysics, and physiology is to become one of the more peripheral subdivisions

The same problem was likewise summarized in the July supplement to the report of the former committee

It is extremely difficult to identify the interests which are both common and peculiar to 'physiologists' of today—interests which are neither the conflicting ones of smaller groups nor those of biological scientists generally in the broadest sense. Over the whole question hangs the specter of the medical biological dichotomy, the tenuous ties across this breach are strained further with every new affiliate to join the Society in the Federation. Another threat is the increasing refusal of special groups to recognize their fields as components of physiology. And pervading all the issues is a disagreement on whether a remedy may be found in an enlargement or a fragmentation of the Society: to some it is too big, to others too small.

Both groups would presumably give affirmative answers to the following questions. These, and the later ones, were circulated to the audience of several hundred that attended this symposium. Ninety replies were received from members of the A P S, fifty-five from non-members (many of whom are members of other Federation societies). These groups also voted affirmatively, mostly strongly so, on all questions. The percentage of "yes" votes is given

	Per cent voting yes	
	Mem bers	Non members
I Should the A P S become more inclusive in its membership?	74	88
By welcoming investigators concerned with functional biology and medicine but not formally physiologists	77	85
By welcoming physiology teachers in colleges and perhaps elsewhere, probably as associate members	77	76
By welcoming students in physiology, not yet established as investigators, as associate or student members	52	64
By welcoming members of other Federation societies, now discouraged from double		

	Per cent voting yes	
	Mem bers	Non members
memberships	51	79
II Should the A P S become actively concerned with the problems, besides research, of physiologists and physiology?	85	95
By creating continuing committees concerned with		
Educational matters	94	94
Economic problems	84	86
Public relations (Societal responsibilities)	83	94
Co operation with other scientific groups	90	100
By sponsoring a physiology section in the A A A S	61	86
By sponsoring an executive secretary and office	79	84

Some further consideration of these is desirable. If the American Physiological Society expands its membership and interests there is the likelihood that it will also change its character. The American Medical Association and the American Chemical Society illustrate both the positive and negative consequences that may flow from such action. A larger membership means more funds and influence and also more dilution of the present intensively directed activity. But failure to expand does not mean retaining the past status, for science and the world are changing. New fragmentations will occur until the American Physiological Society becomes a small fragment of some other group, as the Federation or the Institute of Biology. As L. F. Briggs wrote (N R C Bimonthly Report Feb 1947) in urging an Institute of Biology,

"The group of about 3,000 who call themselves the Federation for Experimental Biology ought to be strengthened and developed beyond the stage of a forum for the presentation of research results and of a common journal, into a strong national society similar to the engineering societies or to the A M A."<sup>1</sup>

In any event, some balance will be achieved between autonomy and participation, it seems to the committee that expansion rather than restriction is the sounder path.

Even so, many of the external problems of physiology are not unique to it but are shared more or less widely by other biological groups. Several of the particular committees suggested would presumably work partly as such, partly through more inclusive groups, as the Institute or the Federation. The economic problems of physiology and physiologists, for example, are to no great

<sup>1</sup> It is a satisfaction to add that, since this material was prepared, the A P S voted unanimously to join the nascent Institute.

extent particular for them, and how effectively and completely these problems could be referred to a larger group, only experience will tell. Some of the matters that should be handled by such committees, whether of the Society or a wider group or both, are suggested here. A Societal Responsibilities Committee dealing with government legislation, relation to the military, science popularization and adult education (lectures, radio, magazine articles, news stories)—e.g., vivisection, biology teaching at lower school levels, etc. An Economic Committee dealing with grants, contracts, fellowships, salaries, jobs, post-doctorate training, industrial relations, technician training, etc. An Inter-Society Relations Committee dealing with other Federation societies, other biological societies, the A A A S, American Institute of Biology, UNESCO, international physiological organizations, etc.

A section on physiology in the American Association for the Advancement of Science, sponsored by the American Physiological Society and separable from existing sections on botany, zoology, or medical sciences, could serve several ends. It would enhance the tenuous relation between the Society and the Association. It would automatically offer a formal meeting, independent of our own annual one, at which reports could be made. The program here could well be selected with an eye on the interests of other participating groups—plant physiologists, experimental psychologists, etc. It could, from another viewpoint, constitute a regional scientific session of the American Physiological Society. Or it could emphasize papers and symposia dealing with educational, societal, and other problems of concern to scientists more broadly as well as to physiologists. Many of these objectives could be attained by an independent meeting of the A P S in addition to the spring Federation meetings.

With or without such an added outlet, if the American Physiological Society is effectively to concern itself with the status of physiology it must make some realistic decisions. Appointed committees of busy men cannot be expected to carry, with continuity and co-ordination, the load that will surely develop. A central office and salaried officer will be imperative (unless supplied through the Federation or Institute). Further, more decisions on policy, and often more difficult ones, will have to be made by the Society as well as by its Council. More business meetings may be required. Your committee is satisfied that the gain will exceed the cost, gain not only in service by the Society to the community, being interested in education, for example, as a good citizen, but also to physiology itself, by recruiting support and men to it, by opening careers for physiologists along new avenues, and the like.

In contrast to the above, certain problems are mainly internal to physiology and must be handled primarily by Society organs. The Council, for example, must be responsible for Society policy—membership, meetings, etc., and the Publication Board is functioning just as it should. There is need, however, strongly indicated in the questionnaire results, for a standing Committee on Education and Training problems. As part of its assignment, your present committee has explored this area a bit more fully.

In the preceding committee's supplementary report, appeared the following recommendation:

The American Physiological Society should undertake a thorough study of the teaching of physiology. This study should define the relationship of a core of fundamental principles (cellular and mammalian) to the manifold fields of application (medicine, aviation, pharmaceuticals, nutrition, public health, industry, physical education, comparative biology, etc.), and recommend methods for obtaining the best possible balance. It should also seek for ways to extend and improve the teaching of human physiology in schools and colleges, not only as an advanced subject in biology and preparation for specialized research, but also as a required course for advanced students in other sciences and as a part of non-scientists' general cultural education. It should formulate recommendations as to the optimal coverage of the medical physiology course and the training which should precede it. This is a big job but its need is widely felt and a positive start should be made on it. As a corollary to this effort, there should be an opportunity for discussion of both the broad and the technical aspects of the teaching of physiology at the Society's meetings.

This outlines well the scope of a committee on education, although it may bear emphasis that it is the responsibility of physiologists to insist that biology teaching at the lower levels be more dynamic and analytic and less descriptive. Biology for citizens involves more than seeing the beautiful birds and flowers. Some of the Committee's possible actions and their outcomes are indicated in the following questions:

- |  | or<br>Mem. Voting<br>bers members |
|--|-----------------------------------|
| Should a regular sectional meeting on teaching (and perhaps other non-research areas) be set up at A P S meetings? | 83 82                             |
| Should time be made at formal business meetings (evening sessions?) for action on committee reports and studies?   | 87 84                             |
| Should special studies be undertaken from time to time of current teaching practices, trends, etc.?                | 91 91                             |
| Should the A P S, on the basis of such studies or otherwise,   |                                   |

	% voting yes	
	Mem	Non
	bers	members
undertake to formulate recommendations?	72	85
Should the A P S concern itself with teaching aids and encourage desired trends?		
Text books	56	83
Hand books	54	81
Laboratory manuals	54	72
Motion pictures	75	95
Exchange of teachers	78	93
Other	37	80
Should the A P S encourage medical schools to require work in physiology for admission? <sup>2</sup>	53	61

If studies were undertaken, the following outlines indicate two directions they might take

A. An observer (or, less good, a questionnaire) might be sent to well selected departments of physiology and such other departments as have a physiological section, to obtain a picture of the status of physiological education. Information along the following lines might be requested:

What are the course examinations and other prerequisites for admission to candidacy for a Ph D in physiology in the department? Are these the same for all students, or do they vary with the student's ultimate objective?

Similarly, what are the requirements for the final awarding of the degree in terms of courses, research, and other achievements, and are these uniform or differentiated?

What courses are actually taught in the department for college students, medical students, graduate students and others?

Answers to this last should be requested in considerable detail, such as a list of the actual lecture topics day by day for the course, of the laboratory experiments called for in similar detail, total hours spent, texts and other reading, types of examinations, teaching techniques, and so on.

Does the department consider the present status satisfactory, or should it be changed? In what directions and details would each department like to see its own work altered, and what views does it have about the desired movement of physiology in the country as a whole?

How much of the present physiology taught to medical students is really necessary for their understanding of medicine and used by them in later years? How much is evanescent detail? This would be a good thought provoking question.

What physiology, or dynamic biology, is included in general education programs and in teacher-training curricula? The scientific habit of a future generation will depend in part, and the

biological understanding almost entirely, on the amount and character of such teaching, as does also the funneling into physiology of its share of top brains. Physiology outstandingly exemplifies the rational and analytic approach to complex problems, which must supersede the still common didactic and descriptive presentation.

B. By an appropriate sampling of physiological publications at intervals of five or ten years for a number of decades, and correlation with other relevant material, factual information should be obtainable to answer such questions as the following:

How closely does research output in any area parallel the financial support within that area?

What is the research cost per page of published work?

Which lines of research have or have not "paid off" in real understanding or valuable application? Can any determining factors be identified?

How has the center of emphasis in physiology shifted over the decades, and what is its present trend?

Examination of publications of the professors of some twenty or thirty leading physiology departments of the world, decade by decade for the last century, might be extremely interesting. They would show, for example, whether the trend has been from physiology and anatomy representing the quantitative and analytical aspect of biology, with zoology and botany representing the classificatory and naturalistic one, and whether this analytical biology has gradually been encroached upon by the other departments, relegating physiology and anatomy more to medical hand-maids. Such a study should point up admirably the basic question of which way physiology is going and whether it should do so.

An attempt to answer such questions or decide on such actions, as have been indicated, is beyond the province of the present committee. Even to press the analysis further was profitless until the Society had indicated the degree of its interest in these various areas. Such an indication to guide the Council's steps toward formal action was obtained at the time of the Symposium.

It is noteworthy that both members (85 percent) and non members (95 percent) are more strongly in favor of the A P S concerning itself with the wider problems of physiology than they are in the case of any other general item on the questionnaire. (This is emphasized by many written-in comments added to the formal vote.) Further, they particularly desire a standing committee on educational matters (94 percent each) and wish it to make special studies on teaching practices, trends, etc. (91 percent each) and, at a more detailed level, to foster the exchange of teachers (78 percent and 93 percent) and the use of teaching motion pictures (75 and 95 percent). The desire seems clear, the means, financial and organizational, must be explored by the Council and the Society. Decisions on these points will help determine the future of the American Physiological Society. Any action of the Society, in turn, will but influence American physiology.

<sup>2</sup> Numerous comments indicate that the yes response would have been much higher, perhaps 80 percent, had the question specified required work in general, not mammalian, physiology. If medical schools required for admission some work in general physiology, about four hundred colleges would introduce or expand courses in this vital area. (Comroe)





## THIRTY-SECOND ANNUAL MEETING

*Atlantic City, New Jersey*

MARCH 15, 16, 17, 18 AND 19, 1948

The 1948 convention of the Federation will be held in Atlantic City, New Jersey, March 15 to 19. The Scientific Sessions of the six constituent Societies will begin Tuesday, March 16, at 9 00 a m. Sunday and Monday, March 14 and 15, will be devoted to meetings of the Federation Executive Committee, the Councils of the Societies and the various committees of the Societies.

The Chalfonte Haddon Hall Hotel will be the Headquarters Hotel for the Federation and the locus of Council and Executive Committee meetings. The scientific sessions and business meetings of the Societies will be held in the Municipal Auditorium. Room locations of these activities will be given in the program of the meeting.

*Hotel Reservations* should be made as soon as possible by addressing Dr M O Lee, Housing Bureau, 16 Central Pier, Atlantic City, New Jersey, and indicating the accommodations desired. Rates at "Boardwalk" Hotels range from \$4 to \$12 for single room with bath, and from \$5 to \$18 for double room with bath. At "Avenue" Hotels, off the Boardwalk, rates range from \$3 50 to \$9, single, and from \$6 to \$12, double. Rooms for groups of three or four persons may be obtained at slightly lower rates. A shortage of hotel accommodations is not anticipated this year.

*Registration* will open at 9 00 a m, on Monday, March 15, at the Municipal Auditorium. The registration desks will be open until 10 00 p m Monday evening, and from 8 00 a m to 5 00 p m on Tuesday, Wednesday, Thursday and Friday.

Members of any of the constituent Societies, guests, and other biologists and physicians who wish to attend the meetings may register. The registration fee will be \$3 00. The official badge, issued at registration, must be worn to secure admission to any of the meetings or other activities of the Convention. A separate registration desk will be located in the foyer of the Auditorium, where ladies who are present as guests may register without charge.

Since the scientific sessions begin promptly at 9 00 a m on Tuesday, it is urged that registration be completed on Monday if possible.

Advance registration by mail will not be available this year, as facilities for handling registration at Atlantic City are adequate.

Programs, abstracts and tickets to various special functions will be on sale in the foyer of the Auditorium. An information booth will also be located in the foyer. The business office of the Federation will be located in Room 8 of the Auditorium.

*An Informal Mixer* is planned for Wednesday evening, March 17, from 9 00 p m until midnight. The official badge issued will be necessary for admission and all who have registered are cordially invited to attend. The Mixer will be held in the arena of the Auditorium.

*Exhibits* No static demonstrations will be held at the Convention. It is planned to hold a commercial exhibit in 1948, for the first time, at which publishers and manufacturers of equipment, apparatus, supplies, chemicals and pharmaceuticals will have their products on display.

*Motion Pictures* will be shown at one session, as scheduled on the program. In addition, it is anticipated that a number of teaching films loaned by the Film Library of the English Physiological Society may be shown.

*Group Dinners and Luncheons* Facilities will be ample for the holding of group dinners or luncheons. In order to avoid conflicts and to provide good service, any group desiring to schedule a dinner or luncheon is requested to make arrangements by writing to Dr M O Lee, 2101 Constitution Ave., Washington 25, D C, stating the number expected to attend and the desired time.

Programs, abstracts and additional announcements will appear in the March 1948 issue of *Federation Proceedings*.

## EXECUTIVE COMMITTEE, 1947-1948

WALLACE O. FLANN, MAURICE B. VISSCHER, The Physiological Society  
 HANS T. CHARKL, OTTO A. BESSLER, The Biochemical Society  
 MAURICE H. SLEEVERS, HARVEY B. HAAC, The Pharmacological Society  
 DOUGLAS H. SPRUNT, FRILDA S. ROBSCHLIT-ROBBINS, The Pathological Society  
 R. M. BETHELL, H. E. CARTER, The Institute of Nutrition  
 LLOYD D. FELTON, ARTHUR F. COCA, The Association of Immunologists  
 MAURICE H. SLEEVERS, *Chairman*, University of Michigan Medical School, Ann Arbor, Michigan  
 A. BAIRD HASTINGS, *Ex Chairman*  
 WILLIAM H. CHAMBERS, *Secretary*, Medical Division, Army Chemical Center, Md

## STANDING COMMITTEES

*Defense of Biological Research* A. C. IVY, *Chairman*, K. F. MLYER, I. PHRAIM SHORR

*International Congresses* D. W. BROWN, *Physiology, Chairman*, A. J. CARLSON, *Physiology*, D. D. VAN SLYKE, *Biochemistry*, H. B. VAN DYKE, *Pharmacology*, PEYTON ROUS, *Pathology*, L. A. MAYNARD, *Nutrition*, J. J. BRONFENBRENNER, *Immunology*

*Placement Service* M. O. LILL, *Director*

*Representatives, Council* A. A. L. S. G. PHILIP GRABFIELD, C. GLEN KING

*Federation Proceedings, Control Committee* PHILIP BARD, *Chairman*, *Physiology*, C. G. KING, *Biochemistry*, McKEEN CATTELL, *Pharmacology*, MORTON McCUTCHEON, *Pathology*, A. H. SMITH, *Nutrition*, A. P. LOCKE, *Immunology*

## FORMER EXECUTIVE COMMITTEES

Philadelphia, Dec 28-31, 1913

S. J. MELTZER, *Chairman*, and A. J. CARLSON, *Secretary*, The Physiological Society A. B. MACALLUM and P. A. SHAFFER, The Biochemical Society T. SOLLMANN and J. AUER, The Pharmacological Society

St. Louis, Dec 27-30, 1914

G. LUSK, *Chairman*, and P. A. SHAFFER, *Secretary*, The Biochemical Society T. SOLLMANN and J. AUER, The Pharmacological Society R. M. PEARCE and G. H. WHIPPLE, The Pathological Society W. B. CANNON and A. J. CARLSON, The Physiological Society

Boston, Dec 26-29, 1915

TORALD SOLLMANN, *Chairman*, and JOHN AUER, *Secretary*, The Pharmacological Society THEOBALD SMITH and PEYTON ROUS, The Pathological Society W. B. CANNON and C. W. GREENE, The Physiological Society WAITER JONES and P. A. SHAFFER, The Biochemical Society

New York, Dec 27-30, 1916

SIMON FLEXNER, *Chairman*, and PEYTON ROUS, *Secretary*, The Pathological Society W. B. CANNON and C. W. GREENE, The Physiological Society WALTER JONES and STANLEY R. BENEDICT, The

Biochemical Society REID HUNT and J. AUER, The Pharmacological Society

Minneapolis-Rochester, Dec 27-29, 1917

FREDERIC S. LEE, *Chairman*, and CHARLES W. GREENE, *Secretary*, The Physiological Society CARL L. ALSBERG, and STANLEY R. BENEDICT, The Biochemical Society REID HUNT and L. G. ROWAN, The Pharmacological Society LUDWIG HILKOF and HOWARD T. KARSNER, The Pathological Society

Baltimore, April 24-26, 1918

CARL L. ALSBERG, *Chairman*, and STANLEY R. BENEDICT, *Secretary*, The Biochemical Society REID HUNT and E. D. BROWN, The Pharmacological Society H. GIDEON WELLS and HOWARD T. KARSNER, The Pathological Society FREDERIC S. LEE and CHARLES W. GREENE, The Physiological Society

Cincinnati, Dec 29-31, 1919

A. S. LOEVENHART, *Chairman*, and E. D. BROWN, *Secretary*, The Pharmacological Society W. G. MACALLUM and HOWARD T. KARSNER, The Pathological Society WARREN P. LOMBARD and CHARLES W. GREENE, The Physiological Society STANLEY R. BENEDICT and VICTOR C. MYERS, The Biochemical Society

Chicago, Dec 28-30, 1920

WILLIAM H. PARK, *Chairman*, and HOWARD T. KARSNER, *Secretary*, The Pathological Society WARREN P. LOMBARD and CHARLES W. GREENE, The Physiological Society STANLEY R. BENEDICT and VICTOR C. MYERS, The Biochemical Society A. S. LOEVENHART and EDGAR D. BROWN, The Pharmacological Society

New Haven, Dec 28-30, 1921

J. J. MACLEOD, *Chairman*, and CHARLES W. GREENE, *Secretary*, The Physiological Society D. D. VAN SLYKE and VICTOR C. MYERS, The Biochemical Society C. W. EDMUNDS and EDGAR D. BROWN, The Pharmacological Society, F. G. NOVY and WADE H. BROWN, The Pathological Society

Toronto, Dec 27-29, 1922

D. D. VAN SLYKE, *Chairman*, and VICTOR C. MYERS, *Secretary*, The Biochemical Society C. W.

EDMUNDS and EDGAR D BROWN, The Pharmacological Society HOWARD T KARSLYR and WADH B BROWN, The Pathological Society, J J R MACLEOD and CHARLES W GREENE, The Physiological Society

St Louis, Dec 27-29, 1923

C W EDMUNDS, *Chairman*, and EDGAR D BROWN, *Secretary*, The Pharmacological Society E L OPIE and WADH B BROWN, The Pathological Society A J CARLSON and CHARLES W GREENE, The Physiological Society PHILIP A SHAEFFER and VICTOR C MYERS, The Biochemical Society

Washington, Dec 29-31, 1924

ALFREDO S WARTHIN, *Chairman*, and E B KRUMBHAR, *Secretary*, The Pathological Society A J CARLSON and WALTER J MEEK, The Physiological Society, P A SHAEFFER and D WRIGHT WILSON, The Biochemical Society JOHN AUER and E D BROWN, The Pharmacological Society

Cleveland, Dec 28-30, 1925

A J CARLSON, *Chairman*, and WALTER J MEEK, *Secretary*, The Physiological Society H C SHIRMAN and D WRIGHT WILSON, The Biochemical Society JOHN AUER and E D BROWN, The Pharmacological Society GEORGE H WHIFFLE and E B KRUMBHAR, The Pathological Society

Rochester, N Y, April 14-16, 1927

E C KENDALL, *Chairman*, and F C KOCH, *Secretary*, The Biochemical Society JOHN AUER and E D BROWN, The Pharmacological Society W H BROWN and E B KRUMBHAR, The Pathological Society J ERLANGER and W J MEEK, The Physiological Society

Ann Arbor, April 12-14, 1928

CARL VOETTLIN, *Chairman*, and E D BROWN, *Secretary*, The Pharmacological Society DAVID MARINE and CARL V WELLER, The Pathological Society JOSEPH ERLANGER and WALTER J MEEK, The Physiological Society E V MCCOLLUM and D WRIGHT WILSON, The Biochemical Society

Boston, Aug 19-24, 1929

(The XIIIth International  
Physiological Congress)

HOWARD B KRUMBHAR, *Chairman*, and CARL V WELLER, *Secretary*, The Pathological Society JOSEPH ERLANGER and WALTER J MEEK, The Physiological Society E V MCCOLLUM and D WRIGHT WILSON, The Biochemical Society CARL VOETTLIN and E D BROWN, The Pharmacological Society

Chicago March 26-29, 1930

WALTER J MEEK, *Chairman*, and ALFRED C REDFIELD, *Secretary*, The Physiological Society W R BLOOR, and HOWARD B LEWIS, The Biochemical Society CARL VOETTLIN and L D BROWN, The Pharmacological Society WILLIAM F PETERSEN and CARL V WELLER, The Pathological Society

Montreal, April 8-11, 1931

W R BLOOR, *Chairman*, and H B LEWIS, *Secretary*, The Biochemical Society GEORGE B WALLACE and E D BROWN, The Pharmacological Society FREDERICK L GATES and C PHILLIP MILLER, The Pathological Society WALTER J MEEK and ARNO B LUCKHARDT, The Physiological Society

Philadelphia, April 27-30, 1932

GEORGE B WALLACE, *Chairman*, and V E HENDERSON, *Secretary*, The Pharmacological Society SAMUEL R HAYTHORN and C PHILLIP MILLER, The Pathological Society WALTER J MEEK and ARNO B LUCKHARDT, The Physiological Society H C BRADLEY and HOWARD B LEWIS, The Biochemical Society

Cincinnati, April 10-12, 1933

PETTON ROUS, *Chairman*, and C PHILLIP MILLER, *Secretary*, The Pathological Society ARNO B LUCKHARDT and FRANK C MANN, The Physiological Society H C BRADLEY and HOWARD B LEWIS, The Biochemical Society WM DEB MACNIDER and V E HENDERSON, The Pharmacological Society

New York, March 28-31, 1934

ARNO B LUCKHARDT, *Chairman*, FRANK C MANN, *Secretary*, and ALEXANDER FORBES, *Treasurer*, The Physiological Society W M CLARK and H A MATTILL, The Biochemical Society W DFB MACNIDER and V E HENDERSON, The Pharmacological Society CARL V WELLER and C PHILLIP MILLER, The Pathological Society

Detroit, April 10-13, 1935

W M CLARK, *Chairman*, H A MATTILL, *Secretary*, and C H FISKE, *Treasurer*, the Biochemical Society CHARLES W GREENE and FRANK C MANN, The Physiological Society R A HATCHER and E M K GEILING, The Pharmacological Society S BURT WOLBACH and SHIELDS WARREN, The Pathological Society

Washington, March 25-28, 1936

V E HENDERSON, *Chairman*, E M K GEILING, *Secretary*, and C M GRUBER, *Treasurer*, The

Pharmacological Society FRANK C MANN and ANDREW C IVY, The Physiological Society H B LEWIS and H A MATTILL, The Biochemical Society OSKAR KLOTZ and SHIELDS WARREN, The Pathological Society

Memphis, April 21-24, 1937

ALIBERT R DOCHET, *Chairman*, and SHIELDS WARREN, The Pathological Society FRANK C MANN and ANDREW C IVY, The Physiological Society HOWARD B LEWIS and H A MATTILL, The Biochemical Society A E HENDERSON and E M K GEILING, The Pharmacological Society D R HOOKER, *Secretary*

Baltimore, March 30-April 2, 1938

WILLIAM T PORTER, *Honorary President*, WALTER E GARREY, *Chairman*, and ANDREW C IVY, The Physiological Society GLENN E CULLEN and H A MATTILL, The Biochemical Society ARTHUR L TATUM and G PHILIP GRABFIELD, The Pharmacological Society C PHILLIP MILLER and PAUL R CANNON, The Pathological Society D R HOOKER, *Secretary*

Toronto, April 26-29, 1939

GLENN E CULLEN, *Chairman*, and CHARLES G KING, The Biochemical Society ARTHUR L TATUM and G PHILIP GRABFIELD, The Pharmacological Society C PHILLIP MILLER and PAUL R CANNON, The Pathological Society WALTER E GARREY and ANDREW C IVY, The Physiological Society D R HOOKER, *Secretary*

New Orleans, March 13-16, 1940

E M K GEILING, *Chairman*, and G PHILIP GRABFIELD, The Pharmacological Society ERNEST W GOODPASTURE and PAUL R CANNON, The Pathological Society ANDREW C IVY and PHILIP BARD, The Physiological Society WILLIAM C ROSE and CHARLES G KING, The Biochemical Society D R HOOKER, *Secretary*

Chicago, April 15-19, 1941

SHIELDS WARREN, *Chairman*, and H P SMITH, The Pathological Society THORNE M CARPENTER and L A MAYNARD, The Institute of Nutrition ANDREW C IVY and PHILIP BARD, The Physiological Society WILLIAM C ROSE and CHARLES G KING, The Biochemical Society E M K GEILING

and G PHILIP GRABFIELD, The Pharmacological Society D R HOOKER, *Secretary*

Boston, March 31, April 1, 2, 3, 4, 1942

ALIBERT R DOCHET, *Chairman*, and ARTHUR H SMITH, The Institute of Nutrition PHILIP BARD and CARL J WIGGERS, The Physiological Society RICHARD J ANDERSON and ARNOLD K BALLS, The Biochemical Society L M K GEILING and R N BIETER, The Pharmacological Society JESSE L BOITMAN and H P SMITH, The Pathological Society SHIELDS WARREN, *Ex Chairman* D R HOOKER, *Secretary*

1943, 1944, 1945 The meetings scheduled for Cleveland were cancelled because of war conditions

PHILIP BARD, *Chairman*, and WALLACE O FENN, The Physiological Society L A DOISE and ARNOLD K BALLS, The Biochemical Society E K MARSHALL, JR and RAYMOND N BIETER, The Pharmacological Society BALDWIN LUCKÉ and H P SMITH, The Pathological Society LEONARD A MAYNARD and ARTHUR H SMITH, The Institute of Nutrition JACQUES J BROUFEUBRENNER and ARTHUR F COCA, The Association of Immunologists D R HOOKER, *Secretary*

Atlantic City, Mar 11, 12, 13, 14, 15, 1946

PHILIP BARD, *Chairman*, WALLACE O FENN, The Physiological Society A BAIRD HASTINGS and ARNOLD K BALLS, The Biochemical Society ERWIN E NELSON and RAYMOND N BIETER, The Pharmacological Society BALDWIN LUCKÉ and H P SMITH, The Pathological Society WILLIAM C ROSE and H E CARTER, The Institute of Nutrition JACQUES J BROUFEUBRENNER and ARTHUR F COCA, The Association of Immunologists D R HOOKER, *Secretary*

Chicago, May 18-22, 1947

A BAIRD HASTINGS, *Chairman*, and OTTO A BESSEY, The Biochemical Society MAURICE H SEEVERS and HARVEY B HAAG, The Pharmacological Society PAUL R CANNON and FRIEDA S ROBSCHT-ROBBINS, The Pathological Society ARTHUR H SMITH and H E CARTER, The Institute of Nutrition MICHAEL HEIDELBERGER and ARTHUR F COCA, The Association of Immunologists WALLACE O FENN and MAURICE B VISSCHER, The Physiological Society WILLIAM H CHAMBERS, *Secretary*

## FEDERATION BY-LAWS

## BY-LAWS

*Adopted at the Washington Meeting, 1936 and amended at the Boston Meeting, 1942*

1 The Presidents and Secretaries of the Constituent Societies, the Chairman of the Executive Committee of the preceding year and the Federation Secretary shall form the Executive Committee of the Federation

2 The Chairmanship of the Executive Committee shall be held in turn by the Presidents of the Constituent Societies, who shall succeed one another annually in the order of seniority of the Societies

3 The Executive Committee shall appoint annually from the membership of the Federation a secretary treasurer, to be known as the Federation Secretary

4 The Federation Secretary shall (a) Keep the minutes of the Executive Committee and distribute copies to the Secretaries of the Constituent Societies (b) Make arrangements for the Annual Meeting with the Local Committee, with the approval of the Executive Committee (c) Print in convenient combined form and distribute to the membership of the Federation the programs of the Constituent Societies as received from their respective Secretaries (d) Undertake such other duties to be decided upon from time to time by the Executive Committee, as do not conflict with the complete autonomy of the Constituent Societies

5 The Executive Committee shall control all monies in the hands of the Federation Secretary, who shall make an annual report to the Executive Committee for audit and approval The expenses of the Federation Secretary, as authorized by the Executive Committee, shall be the first charge on such monies and if insufficient for the purpose the Executive Committee shall prorate such expenses to the Constituent Societies of the Federation in proportion to their respective memberships

The Executive Committee may appropriate Federation monies annually for the uses of Local Committees and for the uses of other authorized Committees but in the latter cases an audit of expenditures shall be made and approved before such committees are discharged

6 The Executive Committee shall determine the place of the Annual Meeting, and the time shall be determined by the Local Committee, preferably within the period of March fifteenth to May first

7 The local Committee at the place of meeting of the Federation shall charge such fee for registration as may be approved by the Executive Committee The monies thus collected shall be used to defray the expenses of the Local Committee and the remainder, after such expenses have been met, shall be turned over to the Federation Secretary

8 The Executive Committee shall consider measures of advantage to the Federation as a whole Any Constituent Society may refer similar measures to the Executive Committee No action, however, shall be taken by the Executive Committee unless specifically authorized by all the Constituent Societies

9 The Chairman of the Executive Committee may appoint committees when the purposes of such committees have been approved by all the Constituent Societies of the Federation Such committees shall be appointed for a term of one year, but may be continued and their members reappointed Such committees shall report in writing to the Executive Committee, which shall in turn report thereon to the Constituent Societies either for information or recommendation The Secretaries of the Constituent Societies shall report the recommendations of their respective Societies to the Executive Committee for final action

10 All individuals whose names appear on the program by invitation or introduction and those registering from any recognized biological laboratory may be enrolled as Associate Members of the Federation for that Annual Meeting Such Associate Members may enjoy all the privileges of the Annual Meeting except that of voting

11 No person may present orally more than one paper during all of the scientific sessions of the Constituent Societies at the time of the Annual Meeting except upon invitation of the Executive Committee or a Council Papers must be submitted to the Secretary of the Society of which the proposer is a member The proposer may request transfer to another program, but this may only be done with the consent of the Secretary of the Society concerned Any Secretary who regards any paper submitted to him as better suited to the program of another Society may arrange this transfer with the Secretary of the Society concerned, if it be possible Such transfer shall be indicated on the program

12 Abstracts not to exceed two hundred and fifty words in length, of papers approved for presentation at all of the scientific sessions of all the Constituent Societies at the Annual Meeting, shall receive publication in the *Federation Proceedings*

13 A Control Committee, consisting of at least one representative of each Constituent Society as designated by the several Councils, shall have editorial control over the *Federation Proceedings* which shall be financed as required by an annual assessment of all the members of each Constituent Society

14 The Control Committee shall have power to

choose certain additional papers presented at the Annual Meetings and from other sources, including material heretofore published in the Federation Yearbook, for publication in the Federation Proceedings

## PLACEMENT SERVICE

The Federation maintains a service to act as a medium of communication between persons seeking positions for teaching or research and institutions that wish to fill vacancies in these sciences

The service does not undertake to recommend or to pass judgment upon applicants. It aims merely to serve as a clearing-house for such information as above stated and to bring into touch

with one another candidates for positions and vacancies to be filled

The Placement Service is being reorganized in line with the recommendations of the Federation Committee for its study, and to utilize certain of the facilities and forms of the Office of Scientific Personnel of the National Research Council. Individuals, whether members of the Federation or not, Universities, other institutions and organizations desiring to avail themselves of the Service may receive such information as is available. By action of the Executive Committee in 1947, a registration fee of one dollar is required of each applicant for a position

All communications should be addressed to Dr. M. O. Lee, Director, Placement Service, 2101 Constitution Ave., Washington 25, D. C.

## THE AMERICAN PHYSIOLOGICAL SOCIETY

*Founded December 30, 1887, Incorporated June 2, 1923*

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## CONSTITUTION

### I

1 This Society shall be named "THE AMERICAN PHYSIOLOGICAL SOCIETY, INCORPORATED"

2 The Society is instituted to promote the advance of Physiology and to facilitate personal intercourse between American Physiologists

### II

1 The Society shall consist of members and honorary members

2 Any person who has conducted and published meritorious original researches in Physiology and who is a resident of North America shall be eligible for membership in the Society

3 Members who have been relieved by the Council of the payment of the annual assessment shall retain all the rights of members

4 Distinguished men of science who have contributed to the advance of Physiology shall be eligible for election as honorary members of the Society. Honorary members shall pay no membership fee. They shall have the right of attending the meetings of the Society, and of taking part in its scientific discussions, but they shall have no vote

### III

1 The management of the Society shall be vested in a Council consisting of the President, Secretary, and Treasurer and four other members to be chosen by ballot at each annual meeting. The President, Secretary, and Treasurer shall be elected for one year. The President shall be subject to only one reelection. The four additional members of the Council shall be elected for a term of four years and the term of office of one of these

Councilors shall expire at the close of each annual meeting. The four additional members of the Council shall not succeed themselves. If the annual meeting is not held all the members of the Council shall continue in office until their successors are chosen in the prescribed manner and succession.

2 The Council shall have power to fill all interim vacancies that may occur in its membership or in any Committee or board of the Society except those for which other provisions have been made.

### IV

1 At least a fortnight before the annual meeting the Secretary shall send to each member a notice of the place and time of each meeting, and shall make such other announcements as the Council shall direct.

2 The annual assessment shall be determined by the Council, and shall be due in advance at the time of the annual meeting. No allocation or disbursement of funds of the Society shall be made except upon prior approval of the Council. Appropriations shall be made by the Council for the conduct of the necessary and appropriate business of the Society.

3 Any member whose assessment is two years in arrears shall cease to be a member of the Society, unless at the next annual meeting he shall be reinstated by special vote of the Society, and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to said meeting.

4 Any member who has retired because of illness or age may, upon application to the Council be relieved from payment of the annual assessment.

### V

1 Meetings of the Society for the conduct of business and the presentation of papers and demonstrations shall be held annually except for national emergencies or other exceptional circumstances when the Council may cancel the proposed meeting. The time and place of such meetings shall be determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology.

2 Special meetings may be held at such times and places as the Council may determine.

### VI

1 Proposed amendments to the Constitution must be brought up at one meeting for preliminary discussion and approval by a majority vote and cannot be adopted except by a two-thirds vote at a business session at the next annual meeting. Notice of such changes shall be sent to all mem-

bers at least two weeks prior to the meeting at which they are scheduled for adoption

2 At all business meetings of the Society twenty-five members shall form a quorum

3 By laws for the conduct of the Society may be adopted, altered, or repealed at any business meeting by two thirds vote of the ballots cast

## VII

1 The Council may, from the names of the candidates proposed in writing by at least two members of the Society, nominate candidates for election to membership. The names of the candidates so nominated and a statement of their qualifications for membership signed by their proposers shall be available for inspection during the business sessions of the Society at which their election is considered. The candidates may be balloted for at any session of the same meeting and a majority vote shall elect. If an annual meeting is not held, the Council shall elect the candidates to membership subject to Society approval at the next annual meeting.

2 Honorary members shall be proposed by the Council, and shall be elected by a majority ballot of the members present at an annual business session of the Society

## VIII

1 If a majority of the Council shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion, and if two-thirds of the members present vote for it, the member shall be expelled, and his assessment for the current year shall be returned to him and he shall cease to be a member of the Society

## IX

1 The official organs of the Society shall be the American Journal of Physiology, the Physiological Reviews and such other publications as the Society shall establish. These the Society shall own and they shall be managed according to the provisions of Article X

## X

1 The President of the Society shall appoint, in consultation with the Council and subject to the approval of the Society, three members of the Society to serve as members of a Board of Publication Trustees

2 The initial appointments shall be for one, two and three years. Thereafter, each member shall be appointed for three years, and shall be eligible for one immediate reappointment. He may be subsequently reappointed, but only after the lapse of at least one year between reappointments

3 The Board of Publication Trustees shall be vested with full power of the Society to control and manage, both editorially and financially, all of the publications owned in whole or in part by the Society, to appoint editorial boards, to appoint and compensate a Managing Editor, and to control all publication funds, none of which, however, may be diverted from support of publications of the Society except by consent of the Council

1 The Board of Publication Trustees shall make a full report to the Council at each annual meeting of the financial condition and publication policy of the Journals or other publications

## BY-LAWS

1 All papers read before the Society shall be limited to a length of ten minutes. No person may orally present more than one paper. In case of joint authorship the name of the individual who will orally present the paper shall stand first

2 Abstracts in duplicate, not to exceed two hundred and fifty words in length, of all papers to be presented at the annual meeting of the Society shall be required by the Secretary for publication in the Federation Proceedings, in accordance with rules approved by the Council

3 The Council shall upon the request of twenty-five members call a regional meeting of the Society at any time and place, for the reading of papers and the promotion of personal intercourse. Such a request shall be made in writing at least six weeks before the proposed date of meeting. Such meeting shall be held in accordance with the Constitution and By-laws of the Society, and if the regular officers of the Society cannot be present the President shall appoint a committee from among the petitioners to conduct the meeting. The Committee through a Secretary chosen by them shall forward an account of the scientific proceedings of the meeting to the official Secretary of the Society for insertion in the minutes. The Secretary of the meeting shall also prepare and transmit to the official Secretary such abstracts of papers read as may be furnished him, and these abstracts shall be published in the Federation Proceedings in accordance with By law No. 2

4 No general business of the Society shall be transacted at such regional meetings

## THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED

*Founded December 6, 1906, Incorporated September 12, 1919*

### OFFICERS, COMMITTEES AND REPRESENTATIVES FOR 1917

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SHAFER, F P UNDERHILL, Councilors 1918 CARL L ALSBERG, President, I P MATHIWS, Vice President, S R BENEDICT, Secretary, H C BRADLEY, Treasurer, W J GILS, ANDREW HUNTER, E V MCCOLLUM, Councilors 1919 STANLEY R BENEDICT, President, D D VAN SLIKE, Vice-President, V C MYERS, Secretary, H C BRADLEY, Treasurer, ANDREW HUNTER, E V MCCOLLUM, L B MENDEL, Councilors 1920 STANLEY R BENEDICT, President, D D VAN SLIKE, Vice President, V C MYERS, Secretary, H C BRADLEY, Treasurer, OTTO FOLIN, WALTER JONES, L B MENDEL, Councilors 1921 DONALD D VAN SLIKE, President, P A SHAFER, Vice-President, V C MYERS, Secretary, H C BRADLEY, Treasurer, S R BENEDICT, OTTO FOLIN, WALTER JONES, Councilors 1922 DONALD D VAN SLIKE, President, P A SHAFER, Vice-President, V C MYERS, Secretary, W R BLOOR, Treasurer, S R BENEDICT, H C BRADLEY, I P MATHIWS, Councilors 1923 PHILIP A SHAFER, President, H C SHERMAN Vice President, V C MYERS, Secretary, W R BLOOR Treasurer, H C BRADLEY, ANDREW HUNTER, I P MATHIWS, Councilors 1924 PHILIP A SHAFER, President, HENRY C SHERMAN, Vice President, D WRIGHT WILSON, Secretary, WALTER R BLOOR, Treasurer, OTTO FOLIN, ANDREW HUNTER, VICTOR C MYERS, Councilors 1925 HENRY C SHERMAN, President, EDWARD C KENDALL, Vice President, D WRIGHT WILSON, Secretary, WALTER R BLOOR, Treasurer, OTTO FOLIN, LAFAYETTE B MENDEL, PHILIP A SHAFER, Councilors 1926 EDWARD C KENDALL, President, ELMER V MCCOLLUM Vice President, FRED C KOCH, Secretary, GLENN E CULLEN, Treasurer, J B COLLIP, EDWARD A DOISI, ALBERT P MATHIWS, Councilors 1927 E V MCCOLLUM, President, W R BLOOR, Vice President, D WRIGHT WILSON, Secretary, G E CULLEN, Treasurer, E A DOISI, F C KOCH, D C VAN SLIKE, Councilors 1928 E V MCCOLLUM, President, W R BLOOR, Vice-President, D WRIGHT WILSON, Secretary, G E CULLEN, Treasurer, WM M CLARK F C KOCH, D D VAN SLIKE, Councilors 1929 W R BLOOR, President, H C BRADLEY, Vice President, H B LEWIS, Secretary, G E CULLEN, Treasurer, W M CLARK, C L A SCHMIDT, P A SHAFER, Councilors 1930 W R BLOOR, President, H C BRADLEY, Vice-President, H B LEWIS, Secretary, G E CULLEN, Treasurer, W M CLARK, P A SHAFER, D W WILSON, Councilors 1931 H C BRADLEY, President, W M CLARK, Vice President, H B LEWIS, Secretary, C H FISKE, Treasurer, W C ROSE, P A SHAFER, D W WILSON, Councilors 1932 H C BRADLEY, President, W M CLARK, Vice President, H B LEWIS, Secretary, C H FISKE, Treasurer, P E HOWE, W C ROSE, D W WILSON, Councilors 1933

W M CLARK, President, H B LEWIS, Vice-President, H A MATTILL, Secretary, C H FISKE, Treasurer, H C BRADLEY, P E HOWE, W C ROSE, Councilors 1934 W M CLARK, President, H B LEWIS, Vice President, H A MATTILL, Secretary, C H FISKE, Treasurer, H C BRADLEY, E A DOISI, P E HOWE, Councilors 1935 H B LEWIS, President, G E CULLEN, Vice-President, H A MATTILL, Secretary, C H FISKE, Treasurer, H C BRADLEY, J B COLLIP, E A DOISI, Councilors 1936 H B LEWIS, President, G E CULLEN, Vice-President, H A MATTILL, Secretary, I B HASTINGS, Treasurer, J B COLLIP, E A DOISI, W C ROSE, Councilors 1937 G E CULLEN, President, W C ROSE, Vice President, H A MATTILL, Secretary, A B HASTINGS, Treasurer, E A DOISI, H B LEWIS, H B VICKERY, Councilors 1938 G E CULLEN, President, W C ROSE, Vice-President, CHARLES G KING, Secretary, A B HASTINGS, Treasurer, H B LEWIS, H A MATTILL, H B VICKERY, Councilors 1939 W C ROSE, President, R J ANDERSON Vice President, CHARLES G KING, Secretary, A B HASTINGS, Treasurer, H B LEWIS, H A MATTILL, G E CULLEN, Councilors 1940 WILLIAM C ROSE, President, RUDOLPH J ANDERSON, Vice President, CHARLES G KING, Secretary, A B HASTINGS, Treasurer, H A MATTILL, GLENN E CULLEN, E A DOISI, Councilors 1941 R J ANDERSON, President, E A DOISI, Vice President, A K BALLS, Secretary, W C STADIE, Treasurer, H B LEWIS, W C ROSE, Councilors 1942 R J ANDERSON, President, E A DOISI, Vice President, A K BALLS, Secretary, W C STADIE, Treasurer, W C ROSE, C A KING, H Y CLARKE, Councilors 1943 E A DOISI, President, A B HASTINGS, Vice President, A K BALLS, Secretary, W C STADIE, Treasurer, W C ROSE, H T CLARKE, R J ANDERSON, Councilors 1944 E A DOISI, President, A B HASTINGS, Vice-President, A K BALLS, Secretary, W C STADIE Treasurer, R J ANDERSON, H T CLARKE, V DU VIGNEAUD, Councilors 1945 A B HASTINGS, President, H T CLARKE, Vice President, A K BALLS, Secretary, W C STADIE, Treasurer, R J ANDERSON, C F CORI, V DU VIGNEAUD, Councilors 1946 A B HASTINGS, President, H T CLARKE, Vice President, OTTO A BESSEY, Secretary, E A EVANS, JR, Treasurer, V DU VIGNEAUD, C F CORI, A K BALLS, Councilors

## CONSTITUTION

### FROM THE ARTICLES OF INCORPORATION

1 The name of the proposed corporation is "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED"

2 The purposes for which this corporat

formed are to further the extension of biochemical knowledge and to facilitate personal intercourse between American investigators in biological chemistry

## BY-LAWS

### ARTICLE I—*Membership*

SECTION 1 *Eligibility for Membership*—Qualified investigators who have conducted and published meritorious original investigations in biological chemistry shall be eligible for membership in the Society

SEC 2 *Nomination*—Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting

SEC 3 *Election to Membership*—A nominee for membership may be voted for by ballot at any meeting of the Society after Council has reported its findings on his eligibility. The eligible candidate shall be reported by the Council as "eligible" or as "eligible and indorsed." B A majority of the ballots cast shall elect

SEC 4 *Forfeiture*—A member who may grant the use of his name for (a) the advertisement of a patent medicine, a proprietary food preparation, or any other commercial article of doubtful value to the public or possibly harmful to the public health, or (b) who may concede its use for the purpose of encouraging the sale of individual samples (of any such product) that he has not examined, shall forfeit his membership

B The Council shall have authority to announce forfeiture of membership, provided that the copy of the charges, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice, shall have been delivered to the member charged with violating the preceding section either personally or mailed to him at his last known address at least thirty days before the date of such hearing

SEC 5 *Expulsion*—Upon the recommendation of the Council any member may be expelled by a majority vote of the total membership at a meeting of the Society, provided that a copy of the charges against him, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice shall have been delivered to him personally or mailed to him at his last known address at least thirty days before the date of such hearing

### ARTICLE II—*Meetings and Quorum*

SECTION 1 *Annual*—The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation

SEC 2 *Special*—A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice President, and must be called at the request of a majority of the Council or fifteen members of the Society. A notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto. The Council shall select the places at which meetings shall be held

SEC 3 *Quorum*—Fifteen members shall constitute a quorum at all meetings of the Society, but in absence of a quorum any number shall be sufficient to adjourn to a fixed date

### ARTICLE III—*Officials*

SECTION 1 *Officers*—The officers shall be a President, a Vice-President, a Secretary, and a Treasurer, who shall be elected annually by the members of the Society

SEC 2 *Council*—A The officers so elected and three additional members, one of whom shall be elected at each annual meeting of the Society to serve a three year term, shall constitute the Board of Directors of the corporation and shall be known as "The Council." (When this provision is first put into effect three members will need to be elected for a one, a two and a three year period.)

B No two members of the Council may be from the same institution, and none of the officers so elected shall be eligible for re election for more than two years except the Secretary and Treasurer, who shall be eligible for re election for five years. The three additional members of the Council shall be ineligible for re election (until after the lapse of one year)

SEC 3 *Duties of Officers*—The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions

SEC 4 *Assistant Treasurer*—A The Council may from time to time appoint a trust company, or some member of the Society, to serve during the pleasure of the Council as Assistant Treasurer, and to act as depositary of the investments and income of the "Christian A. Herter Memorial Fund" and of such other funds as the Society may from time to time commit to its or his charge

B The Assistant Treasurer shall have and exercise the following powers and duties, viz, the custody and safe-keeping of securities and cash belonging to the "Christian A. Herter Fund" and the collection of income and other moneys due to the Fund, with power to receipt for the same and to endorse for deposit all checks payable to the Society or the Treasurer, or to the Journal of Biological Chemistry for income or other moneys due to the Fund, the investment or reinvestment of the capital of the Fund, subject to the approval of the Council, the disbursement of principal under

the direction of the Council and the disbursement of income under the direction of the Editorial Board of the Journal of Biological Chemistry, such disbursement to be made under a resolution of the Council or Board, or with the approval of two members of either the Council or Board, as the case may be. The Assistant Treasurer shall keep books of account and render statements, annually or oftener upon the request of the Council or Board setting forth the condition of the Fund and the receipts and disbursements since the date of the preceding statement.

#### ARTICLE IV—*The Council*

SECTION 1 *Powers*—The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Directors of a membership corporation by the Membership Corporation Law of the State of New York.

SEC 2 *Reports*—The Council shall report to the Society as promptly as possible its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws.

SEC 3 *Journal of Biological Chemistry*—The Council shall have power to appoint the persons to act as proxies for the Society at all meetings of the stockholders of the "Journal of Biological Chemistry" (a corporation) of which all the stock is owned by the Society, and also to designate the persons to be elected as Directors of such corporation.

SEC 4 *Herter Fund*—It shall be the duty of the Council to see that the "Christian A. Herter Memorial Fund" is administered in accordance with the terms of the Trust Agreement, Dated May 16, 1911, executed by the Journal of Biological Chemistry and the donors of said Fund.

#### ARTICLE V—*Nominating Committee*

SECTION 1 *Membership*—A The Nominating Committee shall consist of nine members from nine different institutions elected at each annual meeting to serve for the ensuing year. Members who have served on the Nominating Committee for two consecutive years shall be ineligible for re-election until after the lapse of one year.

B The member of the Nominating Committee who is elected to the Committee by the largest number of votes shall become Chairman and Secretary of the Committee.

SEC 2 *Nomination of Officials*—A The Nominating Committee shall make at least one nomination for each of the four offices and for each of the three additional positions in the Council to be filled by vote of the members.

B The nominations by the Nominating Committee must be transmitted to the Secretary at least one month before the annual meeting at which they are to be considered.

C The Secretary shall send to every member, at least two weeks before the annual meeting, two copies of the list of nominees presented to him by the Nominating Committee and at the same time shall notify all the members that they may vote by proxy.

D At the opening of the first executive session of the ensuing annual meeting the Secretary shall formally present the regular nominations for the Nominating Committee.

E Additional nominations for the offices and for membership in the Council may be made by any member at the opening of the first executive session of any annual meeting.

F Nominations for membership on the Nominating Committee shall be made by or for individual members, either in person or by proxy, and not otherwise, at the opening of the first executive session of any annual meeting.

SEC 3 *Election of Officials*—A The Secretary shall receive and present to the tellers, appointed by the President to take charge of the election, all signed ballots forwarded by absent members. When such ballots are presented to the tellers the Secretary shall announce the names of the members voting by proxy, and he shall record the same names in the minutes of the meeting.

B All elective officials shall be selected by ballot at the close of the first executive session of each annual meeting.

C A majority of the votes cast shall be necessary to elect an official.

D Elective officials shall take office on July 1st following the annual meeting.

SEC 4 *Filling of Vacancies*—A The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society.

B The President of the Society shall fill all vacancies in appointive positions.

#### ARTICLE VI—*Financial*

SECTION 1 *Dues*—Annual assessments shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due January 15th in each year. Members who have reached the age of 65 years, or who have become incapacitated, may, by vote of the Council, be exempted from the payment of dues.

SEC 2 *Expenditures*—No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council, but this section shall not apply to expen-



ditures from the "Christian A. Herter Memorial Fund"

SEC 3 *Privileges of Membership Begin with Payment of Dues*—Candidates for membership, if elected, shall not be entitled to any of the privileges of membership, before they pay the dues of the fiscal year succeeding their election

SEC 4 *Penalty for Non-Payment of Dues*—A Member in arrears for dues for a period of three consecutive years shall thereupon forfeit their membership

B Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated

SEC 5 *Herter Fund*—The "Christian A. Herter Memorial Fund" shall be held and invested separately from the general funds of the Society and the income thereof shall be expended under the direction of the Editorial Board exclusively for the maintenance and support of the Journal of Biological Chemistry, subject to the supervision and control of the Editorial Committee in accordance with the terms of the Trust Agreement mentioned in ARTICLE IV, SECTION 4, and the provisions of Article VII of the By-Laws

ARTICLE VII—*Journal of Biological Chemistry*

SECTION 1 *Editorial Committee*—There shall be an Editorial Committee consisting of nine members of the Society who shall be nominated by the Nominating Committee and elected by the Society in the same manner as officers. The nine members first elected shall divide themselves by lot into three classes of three in each class, to serve for two, four, and six years respectively, and thereafter three members shall be elected at each alternate annual meeting of the Society to succeed the members of the outgoing class and to serve for a term of six years. Members of the Committee shall be eligible to re-election

SEC 2 *Powers of Committee*—The Committee shall have power to elect an Editorial Board and shall have final authority in matters pertaining to the general policy of the Journal

SEC 3 *Editorial Board*—The members of the Board shall hold office until their successors are elected and shall appoint a Managing Editor from among their own number who shall have direct responsibility and authority for the active editorial conduct of the Journal, and who shall have discretionary power in arranging the details as to the conduct of the Journal. The expenditures of the income of the "Christian A. Herter Memorial Fund" shall be under the direction of the Board, and the approval of any two members of the Board shall be a sufficient warrant to authorize payments from such income

ARTICLE VIII—*Papers on Scientific Subjects*

SECTION 1 *Presentation of Papers*—The Secretary shall request each member who signifies his intention of reading a paper at any session to specify the length of time which its presentation will require. The time thus specified shall be printed on the official program, and the presiding officer shall have no authority to extend it unless a majority of the members present signify their wish to the contrary. In the absence of any specification of time required not more than ten minutes shall be allotted for the reading of any one paper

SEC 2 *Number of Papers*—No member shall be permitted to present more than one paper, either alone or in collaboration, until every member shall have had the opportunity of presenting one paper

ARTICLE IX—*Corporate Seal*

SECTION 1 The corporate seal of the corporation shall be a circle surrounded by the words, "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS," and including the word, "INCORPORATED"

ARTICLE X—*Amendments*

SECTION 1 *Amendments*—These By-Laws, after having been approved by the Council, and adopted by the Society at its first annual meeting, shall not be amended except as hereinafter provided

SEC 2 *Manner of Presentation*—Proposed amendments to the By-Laws must be sent to the Secretary at least one month before the date of the meeting at which they are to be considered and must be endorsed in writing by at least three members

SEC 3 *Notice of Intended Amendments*—The Secretary shall give every member notice of proposed amendments at least two weeks before the meeting at which they are to be considered and shall notify all members that they may vote by proxy

SEC 4 *Adoption of Amendments*—A The Secretary shall receive and present to the tellers appointed by the President all signed ballots forwarded by absent members. When such ballots are presented to the tellers, the Secretary shall announce the names of members voting by proxy, and he shall record the same names in the minutes of the meeting

B Votes upon amendments shall be cast at the opening of the second executive session of the meeting at which they are considered

C Affirmative votes from three fifths of the members voting shall be required for the adoption of an amendment

# AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED

*Founded December 28, 1908, Incorporated June 19, 1933*

## OFFICERS, 1917-1948

*President*—MAURICE H. SLEAVERS, University of Michigan Medical School, Ann Arbor, Mich

*Vice President*—CARL A. DRAGSTEDT, Northwestern University Medical School, Chicago, Ill

*Secretary*—HARVEY B. HAAG, Medical College of Virginia, Richmond, Va

*Treasurer*—K. K. CHEN, Lilly Research Laboratories, Indianapolis, Ind

*Council*—HAMILTON H. ANDERSON, University of California Medical School, San Francisco, JOHN C. KRANTZ, Jr., University of Maryland Medical School, Baltimore, MAURICE H. SEEVERS, CARL A. DRAGSTEDT, HARVEY B. HAAG, K. K. CHEN

*Membership Committee*—CARL F. SCHMIDT (term expires 1948), University of Pennsylvania Medical School, Philadelphia 4, CHARLES M. GRUBER (term expires 1949), Jefferson Medical College, 1025 Walnut St., Philadelphia, Pa., ROBERT P. WALTON (term expires 1950), Medical College of the State of South Carolina, Charleston

*Nominating Committee*—R. A. WOODBURY, Chairman, C. J. CARR, CARL C. PFEIFFER, PETER K. KNOEFEL, B. H. ROBBINS

## PAST OFFICERS

1909 J. J. ABEL, President, REID HUNT, Secretary, A. S. LOEVENHART, Treasurer, S. J. MELTZER, T. SOLLMANN, C. W. EDMUNDS, A. C. CRAWFORD, Councilors 1910 J. J. ABEL, President, REID HUNT, Secretary, A. S. LOEVENHART, Treasurer, A. C. CRAWFORD, G. B. WALLACE, Councilors 1911 J. J. ABEL, President, REID HUNT, Secretary, A. S. LOEVENHART, Treasurer, G. B. WALLACE, W. DEB. MACNIDER, Councilors 1912 J. J. ABEL, President, J. AUER, Secretary, A. S. LOEVENHART, Treasurer, G. B. WALLACE, REID HUNT, Councilors 1913 T. SOLLMANN, President, J. AUER, Secretary, A. S. LOEVENHART, Treasurer, J. J. ABEL, W. DEB. MACNIDER, Councilors 1914 T. SOLLMANN, President, J. AUER, Secretary, W. DEB. MACNIDER, Treasurer, J. J. ABEL, A. S. LOEVENHART, Councilors 1915 T. SOLLMANN, President, J. AUER, Secretary, W. DEB. MACNIDER, Treasurer, WORTH HALE, D. E. JACKSON, Councilors 1916 REID HUNT, President, J. AUER, Secretary, W. DEB. MACNIDER, Treasurer, A. D. HIRSCHFELDER, G. B. ROTH, Councilors 1917 REID HUNT, President, L. G. ROWNTREE, Secretary, W. DEB. MACNIDER, Treasurer, J. AUER, CARL VOEGTLIN, Councilors 1918 REID HUNT, President, E. D. BROWN, Secre-

tary, W. DEB. MACNIDER, Treasurer, HUGH MCGUIGAN, CARL VOEGTLIN, Councilors 1919 A. S. LOEVENHART, President, E. D. BROWN, Secretary, W. DEB. MACNIDER, Treasurer, REID HUNT, E. K. MARSHALL, Jr., Councilors 1920 A. S. LOEVENHART, President, E. D. BROWN, Secretary, W. DEB. MACNIDER, Treasurer, D. E. JACKSON, E. K. MARSHALL, Jr., Councilors 1921 C. W. EDMUNDS, President, E. D. BROWN, Secretary, HUGH MCGUIGAN, Treasurer, JOHN AUER, J. P. HANZLIK, Councilors 1922 C. W. EDMUNDS, President, E. D. BROWN, Secretary, HUGH MCGUIGAN, Treasurer, J. P. HANZLIK, H. G. BARBOUR, Councilors 1923 C. W. EDMUNDS, President, E. D. BROWN, Secretary, HUGH MCGUIGAN, Treasurer, J. P. HANZLIK, H. G. BARBOUR, Councilors 1924 JOHN AUER, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, J. P. HANZLIK, H. G. BARBOUR, Councilors 1925 JOHN AUER, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, H. G. BARBOUR, W. DEB. MACNIDER, Councilors 1926 JOHN AUER, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, H. G. BARBOUR, W. DEB. MACNIDER, Councilors 1927 CARL VOEGTLIN, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, V. E. HENDERSON, C. W. EDMUNDS, Councilors 1928 CARL VOEGTLIN, President, E. D. BROWN, Secretary, A. L. TATUM, Treasurer, V. E. HENDERSON, C. W. EDMUNDS, Councilors 1929 CARL VOEGTLIN, President, E. D. BROWN, Secretary, O. H. PLANT, Treasurer, V. E. HENDERSON, C. W. EDMUNDS, Councilors 1930 GEORGE B. WALLACE, President, E. D. BROWN, Secretary, O. H. PLANT, Treasurer, H. G. BARBOUR, C. M. GRUBER, Councilors 1931 GEORGE B. WALLACE, President, VELIEN E. HENDERSON, Secretary, O. H. PLANT, Treasurer, PAUL D. LAMSON, WILLIAM DEB. MACNIDER, Councilors 1932 WM. DEB. MACNIDER, President, A. N. RICHARDS, Vice President, V. E. HENDERSON, Secretary, O. H. PLANT, Treasurer, G. B. ROTH, A. L. TATUM, Councilors 1933 WM. DEB. MACNIDER, President, A. L. TATUM, Vice President, V. E. HENDERSON, Secretary, O. H. PLANT, Treasurer, C. M. GRUBER, G. B. ROTH, Councilors 1934 R. A. HATCHER, President, A. L. TATUM, Vice President, E. M. K. GEILING, Secretary, O. H. PLANT, Treasurer, WM. DEB. MACNIDER, R. L. STEHLE, Councilors 1935 V. E. HENDERSON, President, O. H. PLANT, Vice President, E. M. K. GEILING, Secretary, C. M. GRUBER, Treasurer, FLOYD DEEDS, M. S. DOOLEY, Councilors 1936 V. E. HENDERSON, President, O. H. PLANT, Vice President, E. M. K. GEILING

Secretary, C M GRUBLER, Treasurer, C W EDMUNDS, G B WALLACE, Councilors 1937 A L TATUM, President, E M K GLILINO, Vice-President, G P GRABFIELD, Secretary, C M GRUBER, Treasurer, V E HENDERSON, M H SLIVERS, Councilors 1938 A L TATUM, President, E M K GEILING, Vice-President, G P GRABFIELD, Secretary, C M GRUBLER, Treasurer, E K MARSHALL, JR, C F SCHMIDT, Councilors 1939 O H PLANT, President, E M K CHING, Vice-President, G P GRABFIELD, Secretary, E E NELSON, Treasurer, A L TATUM, C A DRAGSTEDT, Councilors 1940 E M K GLILINO, President, C F SCHMIDT, Vice-President, G P GRABFIELD, Secretary, E E NELSON, Treasurer, B H ROBBINS, C H THILNIS, Councilors 1941 E M K GEILING, President, C F SCHMIDT, Vice-President, RAYMOND N BIELER, Secretary, E E NELSON, Treasurer, E G GROSS, R G SMITH, Councilors 1942 E K MARSHALL, JR, President, CARL A DRAGSTEDT, Vice-President, RAYMOND N BIELER, Secretary, E E NELSON, Treasurer, McK CATTELL, R G SMITH, Councilors 1943 E K MARSHALL, JR, President, CARL A DRAGSTEDT, Vice-President, RAYMOND N BIELER, Secretary, E E NELSON, Treasurer, McK CATTELL, R G SMITH, Councilors 1944 E E NELSON, President, C M GRUBER, Vice-President, R N BIELER, Secretary, McKEN CATTELL, Treasurer, HARRY BECKMAN, NATHAN B EDDY, Councilors 1945 E E NELSON, President, C M GRUBER, Vice-President, R N BIELER, Secretary, McKEN CATTELL, Treasurer, HARRY BECKMAN, NATHAN B EDDY, Councilors 1946 MAURICE H SIEVERS, President, H B VAN DYKE, Vice-President, HARVEY B HAAO, Secretary, McKEN CATTELL, Treasurer, HAMILTON H ANDERSON, JOHN C KRANTZ, JR, Councilors

## CONSTITUTION

### ARTICLE I—Name

The name of this organization shall be the "AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED"

### ARTICLE II—Objects

The purpose of this Society shall be to promote these branches of science and to facilitate personal intercourse between investigators who are actively engaged in research in these fields

### ARTICLE III—Membership

SECTION 1 Any person who has conducted and published a meritorious investigation in pharmacology or experimental therapeutics, and who is an active investigator in one of these fields, shall be eligible to membership, subject to the conditions of the other sections of Article III

SEC 2 A Candidates for membership to this Society shall be proposed by two members who are not members of the Council The names so pro-

posed shall be sent to the Secretary at least three months prior to the Annual Meeting

B The Membership Committee shall investigate the qualifications of the candidates and report to the Council

C Candidates reported upon by the Membership Committee to the Council may be recommended for admission by the Council only provided they have been approved by four fifths of the combined membership of the Membership Committee and the Council

D The names of the candidates recommended for admission by the Council shall be posted by the Secretary not later than the day preceding the election for members

E The election of members shall be by individual ballot, one opposing vote in every eight cast shall be sufficient to exclude a candidate from membership

### SEC 3 Forfeiture of Membership

A Any member whose assessment is three years in arrears shall cease to be a member of the Society, unless he shall be reinstated by a special vote of the Council, and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to the Council

B If the Council shall decide that it is for the best interests of the Society that a member be expelled, the member shall be notified and given an opportunity of a hearing before the Council Upon the recommendation of the Council the member then may be expelled by a three-fourths vote of those present at a regular meeting of the Society

### SEC 4 Honorary Members

A Distinguished men of science who have contributed to the advance of pharmacology or experimental therapeutics shall be eligible for election as honorary members of the Society

B Nominations for honorary members shall take the same course as nominations for ordinary members (Art III, Sec 2), but their election shall require the unanimous vote of the members present at the election

C Honorary members shall pay no membership fee They shall have the right to attend all meetings of the Society, and to take part in its discussions, but they shall have no vote

D The conditions for continuation of membership shall be the same for honorary as for ordinary members (Art III, Sec 3), except that forfeiture for arrears of fees does not apply to honorary members

### ARTICLE IV—Officers and Elections

SECTION 1 The management of the Society shall be vested in a Council of six officers, consisting of a

President, a Vice-President, a Secretary, a Treasurer, and two additional members

SEC 2 There shall be a Membership Committee consisting of three members, and a Nominating Committee consisting of five members. No two members of either Committee shall be from the same institution

SEC 3 Members of the Council shall serve for one year but they shall be eligible for re-election

SEC 4 The election of the Membership Committee shall be held annually at the time when the election of officers occurs. At the first meeting of the Society under this Constitution, one member shall be elected to serve on the Committee for three years, one for two years, and one for one year, and subsequently one member shall be elected each year to serve for a period of three years

SEC 5 A Members of the Nominating Committee shall serve for one year. They are eligible for re-election, but shall not hold membership in the Committee for more than two consecutive years

B The Nominating Committee shall make at least one nomination for each office and for position on the Membership Committee to be filled by vote of the members. The nominations so made shall be transmitted to the Secretary and by him in turn to the members, at least one month before the annual meeting. Additional nominations may be made by any member at the time of the annual meeting

C Nominations for membership on the Nominating Committee shall be made by individual members at the time of the annual election. The five nominees who receive the highest number of votes shall be declared elected. The Nominating Committee shall select its own chairman who shall also serve as secretary to the Committee

SEC 6 The election of officers shall be held at the close of the first session of the annual meeting. In voting there shall be a ballot in regular order for each office to be filled, and the majority of the votes cast shall be necessary to a choice

SEC 7 Such vacancies as may occur in the offices and in the various committees in the interval between annual meetings shall be filled by a majority vote of the Council

#### ARTICLE V — *Meetings*

SECTION 1 The annual meeting of the Society shall be held at a time and place determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology

SEC 2 Special meetings may be held at such times and places as the Council may determine

SEC 3 At least four weeks before the annual meeting the Secretary shall send to each member a notice of the time and place of such meeting and

shall make such announcements as the Council may direct

#### ARTICLE VI — *Financial*

SECTION 1 The annual assessment shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due in advance at the time of the meeting

SEC 2 Beyond the ordinary expenditures required by the routine business of the Society no money shall be disbursed save by the authority of the Council or Society

SEC 3 The treasurer shall make an annual report to the Society

SEC 4 In case any profits result to the Society from the Journal of Pharmacology and Experimental Therapeutics at the end of the financial year, such profits shall be kept in a special account, after deducting any sums expended by the Society during the year for the conduct of the Journal, and shall be held subject to the order of the Council on recommendation of the Editorial Board

#### ARTICLE VII — *Quorum*

Ten members shall constitute a quorum for the transaction of business

#### ARTICLE VIII — *By Laws*

By Laws shall be adopted, altered or repealed at any meeting by two thirds vote of the ballots cast

#### ARTICLE IX — *Amendments*

SECTION 1 Intended amendments to the Constitution shall be sent to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be indorsed in writing by at least three members

SEC 2 The Secretary shall give all members due notice of proposed amendments

SEC 3 A four-fifths vote of the members present shall be required for the adoption of an amendment

#### ARTICLE X — *Journal*

SECTION 1 The official publication of the Society shall be the Journal of Pharmacology and Experimental Therapeutics

SEC 2 The Society shall elect an Editor-in-Chief for a term of three years and he with the approval of the Council shall appoint an Editorial Board of six members for a term of three years

SEC 3 The Editorial Board shall have direct authority and responsibility for the active editorial conduct of the Journal of Pharmacology and Experimental Therapeutics and shall have discretionary power in arranging details as to the conduct of the Journal

## BY-LAWS

1 Papers to be read shall be submitted by the members of the Society to the Secretary, who, with the President, shall be empowered to arrange the program. No person may orally present more than one paper. In case of joint authorship, the name of the individual who will orally present the paper shall stand first. Papers not read shall appear on the program as read by title.

2 An abstract of a paper to be read before the Society shall be sent to the Secretary with the title. As early as possible after each meeting, the Secretary shall edit and publish the Proceedings of the Society together with abstracts in a publication authorized by the Society.

3 All applications for membership shall be accompanied by a copy of as many reprints as possible of the published work of the applicant.

## THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

*Founded December 29, 1913*

## OFFICERS, 1947-1948

*President*—DOUGLAS H. SPRUNT, University of Tennessee, Memphis, Tenn.

*Vice-President*—H. P. SMITH, Columbia University, College of Physicians and Surgeons.

*Secretary-Treasurer*—FRIEDA S. ROBSCHT-ROBBINS, University of Rochester School of Medicine, Rochester, N. Y.

*Councilors*—JAMES F. RINEHART, University of California Medical School, San Francisco, Calif., JOHN G. KIDD, Cornell University Medical College, New York, N. Y.

*Representative in the Division of Medical Sciences of the National Research Council*—(July 1, 1916-June 30, 1949) H. P. SMITH, College of Physicians and Surgeons, Columbia Univ., New York, N. Y.

*Representatives on the Council of the American Association for the Advancement of Science*—MALCOLM H. SOULE, Univ. of Michigan, E. B. KRUMBHAR, University of Pennsylvania (terms until June 30, 1949).

*Representative on the Council of the Union of American Biological Societies*—H. P. SMITH, Columbia Univ., College of Physicians and Surgeons, New York, N. Y.

*Representatives on the Eli Lilly Award Committee* (Jointly with the Society of American Bacteriologists)—For nominations: MORTON MCCUTCHEON, Univ. of Pennsylvania; For Award: SHIELDS WARREN, Harvard University.

*Representative on the Committee for the Placement Service*—DOUGLAS H. SPRUNT, Univ. of Tennessee Medical School, Memphis, Tenn.

*Representative in the Division of Medical Sciences of the National Academy of Sciences*—H. P. SMITH, Columbia Univ., College of Physicians and Surgeons, New York, N. Y.

## PAST OFFICERS

1914 R. M. PEARCE, President, JOHN F. ANDERSON, Vice-President, G. H. WHIPPLE, Secretary-

Treasurer, HARVEY CUSHING, DAVID MARINE, Councilors. 1915 THEOBALD SMITH, President, G. H. WHIPPLE, Vice-President, PEYTON ROUS, Secretary-Treasurer, DAVID MARINE, R. M. PEARCE, Councilors. 1916 SIMON FLENNER, President, LEO LOEB, Vice-President, PEYTON ROUS, Secretary-Treasurer, DAVID MARINE, R. M. PEARCE, Councilors. 1917 LUDVIG HEKTOEN, President, LEO LOEB, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, PAUL A. LEWIS, L. G. ROWNTREE, Councilors. 1918 H. GIDEON WELLS, President, W. G. MACCALLUM, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, L. G. ROWNTREE, LUDVIG HEKTOEN, Councilors. 1919 W. G. MACCALLUM, President, WILLIAM H. PARK, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, LUDVIG HEKTOEN, E. L. OPIE, Councilors. 1920 WILLIAM H. PARK, President, F. G. NOVY, Vice-President, HOWARD T. KARSNER, Secretary-Treasurer, E. L. OPIE, WADE H. BROWN, Councilors. 1921 F. G. NOVY, President, HOWARD T. KARSNER, Vice-President, WADE H. BROWN, Secretary-Treasurer, PAUL A. LEWIS, A. R. DOCHETZ, Councilors. 1922 HOWARD T. KARSNER, President, EUGENE L. OPIE, Vice-President, WADE H. BROWN, Secretary-Treasurer, A. R. DOCHETZ, GEORGE H. WHIPPLE, Councilors. 1923 EUGENE L. OPIE, President, ALDRED S. WARTHIN, Vice-President, WADE H. BROWN, Secretary-Treasurer, GEORGE H. WHIPPLE, H. GIDEON WELLS, Councilors. 1924 ALDRED S. WARTHIN, President, GEORGE H. WHIPPLE, Vice-President, EDWARD B. KRUMBHAR, Secretary-Treasurer, H. GIDEON WELLS, FREDERICK L. GATES, Councilors. 1925 GEORGE H. WHIPPLE, President, WADE H. BROWN, Vice-President, EDWARD B. KRUMBHAR, Secretary-Treasurer, FREDERICK L. GATES, DAVID MARINE, Councilors. 1926 WADE H. BROWN, President, DAVID MARINE, Vice-President, EDWARD B. KRUMBHAR, Secretary-Treasurer, FREDERICK L. GATES, WILLIAM F. PETERSEN,

Councilors 1927 DAVID MARINE, President, EDWARD B KRUMBHAR, Vice President, CARL V WELLER, Secretary-Treasurer, WILLIAM F PETERSEN, FREDERICK L GATES, Councilors 1928 EDWARD B KRUMBHAR, President, WILLIAM F PETERSEN, Vice President, CARL V WELLER, Secretary-Treasurer, FREDERICK L GATES, SAMUEL R HAYTHORN, Councilors 1929 WILLIAM F PETERSEN, President, FREDERICK L GATES, Vice-President, CARL V WELLER, Secretary-Treasurer, SAMUEL R HAYTHORN, PLYTON ROUS, Councilors 1930 FREDERICK L GATES, President, SAMUEL R HAYTHORN, Vice President, C PHILLIP MILLER, Secretary-Treasurer, PLYTON ROUS, CARL V WELLER, Councilors 1931 SAMUEL R HAYTHORN, President, PLYTON ROUS, Vice President, C PHILLIP MILLER, Secretary-Treasurer, CARL V WELLER, S BURT WOLBACH, Councilors 1932 PLYTON ROUS, President, CARL V WELLER, Vice-President, C PHILLIP MILLER, Secretary-Treasurer, S BURT WOLBACH, OSKAR KLOTZ, Councilors 1933 CARL V WELLER, President, S BURT WOLBACH, Vice President, C PHILLIP MILLER, Secretary-Treasurer, OSKAR KLOTZ, ALPHONSE R DOCHEZ, Councilors 1934 S BURT WOLBACH, President, OSKAR KLOTZ, Vice-President, SHIELDS WARREN, Secretary-Treasurer, C PHILLIP MILLER, ALPHONSE R DOCHEZ, Councilors 1935 OSKAR KLOTZ, President, ALPHONSE R DOCHEZ, Vice President, SHIELDS WARREN, Secretary-Treasurer, MORTON McCUTCHEON, C PHILLIP MILLER, Councilors 1936 ALPHONSE R DOCHEZ, President, C PHILLIP MILLER, Vice-President, SHIELDS WARREN, Secretary-Treasurer, MORTON McCUTCHEON, ERNEST W GOODPASTURE, Councilors 1937 C PHILLIP MILLER, President, MORTON McCUTCHEON, Vice-President, PAUL R CANNON, Secretary-Treasurer, ERNEST W GOODPASTURE, SHIELDS WARREN, Councilors 1938 MORTON McCUTCHEON, President, ERNEST W GOODPASTURE, Vice President, PAUL R CANNON, Secretary-Treasurer, SHIELDS WARREN, JESSE L BOLLMAN, Councilors 1939 ERNEST W GOODPASTURE, President, SHIELDS WARREN, Vice-President, PAUL R CANNON, Secretary-Treasurer, JESSE L BOLLMAN, BALDUIN LUCKÉ, Councilors 1940 SHIELDS WARREN, President, JESSE L BOLLMAN, Vice President, H P SMITH, Secretary-Treasurer, BALDUIN LUCKÉ, PAUL R CANNON, Councilors 1941 JESSE L BOLLMAN, President, BALDUIN LUCKÉ, Vice-President, H P SMITH, Secretary-Treasurer, PAUL R CANNON, DOUGLAS H SPRUNT, Councilors 1942, 1943, 1944, 1945 BALDUIN LUCKÉ, President, PAUL R CANNON, Vice-President, H P SMITH, Secretary-Treasurer, DOUGLAS H SPRUNT, FRIEDA S ROBSCHT ROBBINS, Councilors 1946 PAUL R CANNON, President, DOUGLAS H SPRUNT, Vice President, FRIEDA S ROBSCHT ROBBINS, Secretary-Treasurer, H P SMITH, JOHN G KIDD, Councilors

SCHMITT ROBBINS, Secretary-Treasurer, H P SMITH, JOHN G KIDD, Councilors

## CONSTITUTION

### ARTICLE I—Name

The Society shall be named "THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY"

### ARTICLE II—Object

The object of this Society is to bring the productive investigators in pathology, working essentially by experimental methods, in closer affiliation with the workers in the other fields of experimental medicine

### ARTICLE III—Time and Place of Meeting

The Society shall meet at the same time and place as the Federation of American Societies for Experimental Biology, which comprises at present the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, the American Society for Experimental Pathology, the American Institute of Nutrition and the American Association of Immunologists

### ARTICLE IV—Membership

SECTION 1 Any American investigator who, through the use of experimental methods, has, within three years prior to his candidacy, contributed meritorious work in pathology, is eligible to membership

SEC 2 It shall be the policy of the Society to restrict its membership to as small numbers as is compatible with the maintenance of an active existence

SEC 3 There shall be two classes of members active and honorary members

*Active members* Candidates for active membership shall be nominated at or before an annual meeting by two members of the Society. The nominators shall present to the Secretary in writing evidence of the candidate's qualifications for membership. Nominations approved by the Council shall be presented to the Society for election at the next annual meeting following nomination. For election a favorable ballot by a majority of the members present is necessary

*Honorary members* These may be elected from the active list or from the group of distinguished investigators at home or abroad who have contributed to the knowledge of pathology by experimental study. They shall be elected only by the unanimous vote of the members present at time of nomination

SEC 4 Active members shall pay such annual dues as are determined upon, from year to year, by

the Council Honorary members shall pay no dues, are not eligible to office, and have no vote in the business affairs of the Society, but they shall have all the privileges of the active members in the scientific proceedings

SEC 5 Upon failure of an active member to pay dues for two years, notice shall be given to the member by the Secretary At the end of the third year, if dues are still unpaid, such failure constitutes forfeiture of membership

SEC 6 A motion for expulsion of a member must be thoroughly investigated by the Council, at this investigation the accused shall be afforded a hearing or may be represented by a member Expulsion can be accomplished only after a unanimous vote by the Council in favor of expulsion, sustained by a four-fifths vote of the members present at the meeting

#### ARTICLE V —Officers

The management of the Society shall be vested in a Council of five members, consisting of a President, a Vice-President, a Secretary-Treasurer, and two other members who shall be nominated by the Council and elected by the Society Officers are elected by a majority vote Vacancies shall be filled by the Council for the unexpired term

The President and Vice President shall hold office for one year and are ineligible for re-election during the following year The Secretary-Treasurer is eligible for re-election Councilors shall hold office for two years and are elected on alternate years At the first election one Councilor shall be elected for a short term of one year

#### ARTICLE VI —Quorum

SECTION 1 —Three constitute a quorum of the Council The Council decides by a majority vote

SEC 2 A quorum of the Society for transaction of business shall be one fourth of the total membership In all questions brought before the Society a majority vote of those present shall decide, except as elsewhere provided for

#### ARTICLE VII —Annual Meeting

SECTION 1 Papers shall be limited to ten minutes However, on motion and with unanimous

consent, the time may be prolonged by a period not exceeding five minutes The Council may make provision for longer papers on suitable occasions

SEC 2 The subjects of papers must be confined to experimental work in pathology In doubtful cases a liberal interpretation by the President and Secretary may prevail The Council may invite, however, presentations dealing with any subject which it considers of considerable interest to the Society

#### ARTICLE VIII —Change of Constitution

A motion concerning a change of the Constitution must be presented to the Council in writing by three members, and must be communicated to the members by the Secretary at least four weeks before the annual meeting At this meeting such a change may be established when accepted by a four fifths vote of the members present

#### BY-LAWS

1 There must be in each year at least one meeting of the Council, which shall take place not later than the evening before the annual meeting

2 At the end of the first session of the annual meeting the Secretary shall read the report of the Council This report shall include (1) names of persons recommended for membership, (2) nominations for offices, (3) matters of general interest The Secretary shall exhibit in a conspicuous place the names of candidates for membership recommended by the Council, together with the evidence of the qualifications of the candidates

3 The election of officers and of new members, changes in the Constitution, etc., shall be voted upon at the end of the first session

4 Changes in the By-Laws may be determined by a majority vote of those present

5 In the year that a new Secretary-Treasurer is elected the incoming Council Member elected that year, or another member of the Council, shall become Assistant Secretary-Treasurer for the duration of the term of the Secretary-Treasurer



## THE AMERICAN INSTITUTE OF NUTRITION

*Founded April 11, 1933, Incorporated November 16, 1934**Member of Federation 1940*

## OFFICERS, 1947-1948

*President*—R M BETHKE, Ohio Agricultural Experiment Station, Wooster, Ohio

*Vice President*—E M NELSON, Food and Drug Administration, Federal Security Agency, Washington 25, D C

*Secretary*—H E CARTER, Nojes Laboratory, Urbana, Ill

*Treasurer*—N R ELLIS, Bureau of Animal Husbandry, U S Department of Agriculture, Beltsville, Md

*Councilors*—D W WOOLLEY, Rockefeller Institute for Medical Research, New York, N Y, H J ALMQUIST, F E Booth Company Laboratories, Emeryville, Calif, A D HOLMES, University of Massachusetts, Amherst, Mass

*Nominating Committee*—HAROLD GOSS, *Chairman*, University of California College of Agriculture, Davis, Calif, H G DAY, Indiana University, Bloomington, Ind, L A MAYNARD, Cornell University, Ithaca, N Y, H P PIERCE, University of Vermont College of Medicine, Burlington, Vt, PEARL SWANSON, Iowa State College, Ames, Iowa

## PAST-OFFICERS

1933 L B MENDEL, President, H C SHERMAN, Vice-President, J R MURLIN, Secretary-Treasurer, E F DuBois, M S ROSE, Councilors 1934 J R MURLIN, President, E F DuBois, Vice-President, ICIE G MACY, Secretary, W M BOOTHBY, Treasurer, A H SMITH, AGNES FAI MORGAN, R M BETHKE, Councilors 1935 J R MURLIN, President, E F DuBois, Vice-President, ICIE G MACY, Secretary, G R COWGILL, Treasurer, A H SMITH, R M BETHKE, L A MAYNARD, Councilors 1936 E F DuBois, President, MARY SWARTZ ROSE, Vice President, G R COWGILL, Treasurer, ICIE G MACY, Secretary, R M BETHKE, L A MAYNARD, C A ELVEHJEN, Councilors 1937 MARY S ROSE, President, E V MCCOLLUM, Vice-President, G R COWGILL, Treasurer, ICIE G MACY, Secretary, L A MAYNARD, C A ELVEHJEN, P E HOWE, Councilors 1938 E V MCCOLLUM, President, T M CARPENTER, Vice President, G R COWGILL, Treasurer, L A MAYNARD, Secretary, C A ELVEHJEN, P E HOWE, HELEN S MITCHELL, Councilors 1939 H C SHERMAN, President, T M CARPENTER, Vice-President, G R COWGILL, Treasurer, L A MAYNARD, Secretary, P E HOWE, HELEN S MITCHELL, A H SMITH, Councilors 1940 THORNE M CARPENTER, President, A G HOGAN,

Vice President, L A MAYNARD, Secretary, W H SEBRELL, JR, Treasurer, HELEN S MITCHELL, ARTHUR H SMITH, LYDIA J ROBERTS, Councilors 1941 A G HOGAN, President, L A MAYNARD, Vice-President, ARTHUR H SMITH, Secretary, W H SEBRELL, JR, Treasurer, T H JUKES, LYDIA J ROBERTS, H B LEWIS, Councilors 1942 L A MAYNARD, President, H B LEWIS, Vice-President, ARTHUR H SMITH, Secretary, W H SEBRELL, JR, Treasurer, LYDIA J ROBERTS, GENEVIEVE STEARNS, T H JUKES, Councilors 1943 H B LEWIS, President, ICIE G MACY-HOOBLER, Vice President, ARTHUR H SMITH, Secretary, LYDIA J ROBERTS, GENEVIEVE STEARNS, T H JUKES, Councilors 1944 ICIE G MACY-HOOBLER, President, WM C ROSE, Vice-President, ARTHUR H SMITH, Secretary, E M NELSON, Treasurer, GENEVIEVE STEARNS, T H JUKES and C A ELVEHJEN, Councilors 1945 WM C ROSE, President, ARTHUR H SMITH, Vice President, H E CARTER, Secretary, E M NELSON, Treasurer, T H JUKES, C A ELVEHJEN, D W WOOLLEY, Councilors 1946 ARTHUR H SMITH, President, R M BETHKE, Vice President, H E CARTER, Secretary, E M NELSON, Treasurer, C A ELVEHJEN, D W WOOLLEY, H J ALMQUIST, Councilors

## CONSTITUTION

1 The name of the proposed society is the "AMERICAN INSTITUTE OF NUTRITION"

2 The purposes of the society are to further the extension of the knowledge of nutrition and to facilitate personal contact between investigators in nutrition and closely related fields of interest

3 The management of the American Institute of Nutrition shall be vested in a council consisting of the President, Vice-President, Secretary, Treasurer and three additional members

## BY-LAWS

## ARTICLE I—Membership

SECTION 1 *Eligibility for membership* Members. Qualified investigators who have independently conducted and published meritorious original investigations in some phase of the chemistry or physiology of nutrition and who have shown a professional interest in nutrition for at least 5 years shall be eligible for membership in the Society

SEC 2 *Nomination* Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary

Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting

SEC 3 *Election to membership* A A nominee for membership may be voted for by ballot at any meeting of the Society after the Council has reported its findings on his eligibility B A majority of the ballots cast shall elect

SEC 4 *Forfeiture* If a majority of the Council after due notice to the member in question and opportunity for a hearing, shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each member at least two weeks before the next annual meeting At this meeting the Secretary shall, on behalf of the Council, propose the expulsion, and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society

## ARTICLE II—Meetings and Quorum

SECTION 1 *Annual* The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation

SEC 2 *Special* A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request in writing of a majority of the Council or fifty members of the Society Notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto The Council shall select the places at which meetings shall be held

SEC 3 *Quorum* Thirty members shall constitute a quorum at all meetings of the Society, but in the absence of a quorum any number shall be sufficient to adjourn to a fixed date

## ARTICLE III—Officials

SECTION 1 *Officers* The officers shall be a President, and a Vice-President, who shall be elected annually, and a Secretary and Treasurer, each of whom shall be elected to serve for a term of three years These officers shall be elected by the members of the Society Their terms of office shall commence on July 1 of the year in which they are elected

SEC 2 *Council* The officers so selected and three additional members, one of whom shall be elected at each annual meeting to serve a term of three years, shall constitute a Board of Trustees and shall be known as 'The Council' (When this provision is first put into effect one member shall be elected for 1 year, one for 2 years and the third for 3 years)

SEC 3 *Duties of Officers* The powers and duties

of the officers elected by the Society shall be such as usually devolve upon their respective positions

## ARTICLE IV—The Council

SECTION 1 *Powers* The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Trustees of an educational institution chartered by the Education Department of the University of the State of New York A permanent charter was issued to the American Institute of Nutrition under date of November 16, 1934

SEC 2 *Reports* The Council shall report to the Society its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws

## ARTICLE V—Nominating Committee

SECTION 1 *Membership* A The Nominating Committee shall consist of five members appointed for the coming year by the retiring President Members who have served on the Nominating Committee for two consecutive years shall be ineligible for reappointment until after a lapse of one year B The President shall designate one member to be Chairman of the Nominating Committee

SEC 2 *Nomination of Officials* A The Nominating Committee shall make at least one nomination for each of the four offices, for each of the additional positions on the Council to be filled by vote of the members and for each of the positions on the Editorial Board to be vacated at the time of the annual meeting Any member of the Institute may submit nominations to the Nominating Committee for its consideration along with those nominations made by the members of the Nominating Committee B The nominations by the Nominating Committee shall be transmitted to the Secretary at least six weeks before the annual meeting at which they are to be considered C The Secretary shall send to every member, at least two weeks before the annual meeting, a printed ballot containing the list of nominees and space for such additional names as the member wishes to propose, and at the same time shall notify the members that they may vote by mail, returning to the Secretary the marked ballot in the envelope provided, at such a time and place as the Secretary may designate, or the ballot may be delivered to the Secretary at the beginning of the business session at which the elections are to take place

SEC 3 *Election of Officials* A At the beginning of the business session the Secretary shall present to the tellers, appointed by the President, the ballots submitted by the members and the ballots

shall be counted forthwith. B A majority of votes cast shall be necessary to elect an official.

SEC 4 *Filling of Vacancies* A The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society. B The President of the Society shall fill all vacancies in appointive positions.

#### ARTICLE VI—*Financial*

SECTION 1 *Dues* The dues shall be the annual cost of subscription to *The Journal of Nutrition* for members plus an annual assessment which shall be determined by majority vote at the annual meetings, upon recommendation of the Council, and shall be due within a month after the annual meeting. A member on attaining the age of 65 may elect to be relieved from all financial obligations to the Institute including subscription to *The Journal of Nutrition*.

SEC 2 *Expenditures* No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council.

SEC 3 *Penalty for non payment of dues* A Members in arrears for dues for two consecutive years shall forfeit their membership. B Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated.

#### ARTICLE VII—*The Journal of Nutrition*

SECTION 1 The American Institute of Nutrition designates *The Journal of Nutrition* as its official organ of publication.

SEC 2 In accordance with the expressed wish of the Wistar Institute of Anatomy and Biology, owner and publisher of *The Journal of Nutrition*, the American Institute of Nutrition shall nominate members of the Editorial Board for its official organ. A The editorial management of *The Journal of Nutrition* shall be vested in an Editorial

Board consisting of an Editor and twelve Board Members. B The Editor shall be chosen by the Editorial Board to serve a term of five years beginning July 1 of the year in which he is chosen, and shall be eligible for reelection. The Editor shall have the power to designate one of the Board Members to serve as his assistant, and such an appointee shall be called Associate Editor. C Three members of the Institute shall be nominated by the Nominating Committee for membership on the Editorial Board each year to serve a term of four years, replacing three retiring members and taking office May 1 of the year in which they are elected. In the event of a vacancy in the membership of the Editorial Board occurring through death or other reason, the Nominating Committee, for each such vacancy to be filled shall make an additional nomination. In this event the nominees elected who receive the greatest number of votes shall serve the longest term of vacancies to be filled. D Retiring members of the Editorial Board shall not be eligible for renomination until one year after their retirement.

#### ARTICLE VIII—*Papers on Scientific Subjects*

SECTION 1 The Secretary shall be authorized to arrange programs for the scientific sessions at the annual meetings.

#### ARTICLE IX—*Changes in Constitution and By Laws*

SECTION 1 Proposed changes in the Constitution and By Laws must be sent in writing to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be signed by at least three members. The Secretary shall send a printed copy of any proposed change to each member at least two weeks before the next meeting and shall notify all members that they may vote by proxy.

SEC 2 If at this meeting two thirds of the votes cast shall favor the proposed change, it shall be made.

## THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

*Founded June 19, 1913, Member of Federation 1942*

#### OFFICERS, 1947-1948

*President*—LLOYD D. FELTON, National Institute of Health, Bethesda 14, Md

*Vice President*—MICHAEL HEIDELBERGER, College of Physicians and Surgeons, 630 West 168th St., New York, N. Y.

*Secretary*—ARTHUR F. COCA, Lederle Laboratories, Pearl River, N. Y.

*Treasurer*—ALFRED J. WEIL, Lederle Laboratories, Pearl River, N. Y.

*Council*—JACQUES J. BRONFENBRENNER, PAUL R. CANNON, GEOFFREY EDSALL, KARL F. MEYER, SANFORD B. HOOKER, *ex officio*

#### PAST OFFICERS

*Presidents*—1913 GERALD B. WEBB 1915 JAMES W. JOBLING 1916 RICHARD WEIL 1917 JOHN A.

KOLMER 1918 WILLIAM H PARK 1919 HANS  
ZINSSER 1920 RUFUS I COLE 1921 FREDERICK  
P GAY 1922 GEORGE W MCCOY 1923 H  
GIDEON WELLS 1924 FREDERICK G NOVY 1925  
WILFRED H MANWARING 1926 LUDVIG HEK-  
TOEN 1927 KARL LANDSTEINER 1928 EUGENE  
L OPIE 1929 OSWALD T AVERY 1930 STANHOPE  
BAYNE-JONES 1931 ALPHONSE R DOZILL 1932  
AUGUSTUS B WADSWORTH 1933 THOMAS M  
RIVERS 1934 FRANCIS G BLAKE 1935 WAR-  
FIELD T LONGCOPE 1936 SANFORD B HOOKER  
1937 CARL TENBROECK 1938 DONALD T FRASER  
1939 GEORGE P BERRY 1940 PAUL R CANNON  
1941 KARL F MEYER 1942-1945 JACQUELS J  
BRONFENBRENNER 1945-1947 MICHAEL HEIDEL-  
BERGER

*Vice-Presidents—1913-1915* GEORGE W ROSS  
1915 GEORGE P SANBORN 1916 JOHN A KOLMER  
*Secretary—1913-1918* MARTIN J SYNOTT  
*Treasurer—1913-1918* WILLARD J STONE  
*Secretary-Treasurer—1918-1915* ARTHUR F  
COCA

## CONSTITUTION

(As revised May, 1947)

### ARTICLE I

SECTION 1 This Association shall be called THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

SECTION 2 The object of the Association shall be to promote the knowledge of immunology, chemo-therapy, virology and related disciplines, and to facilitate contact between investigators in those and related fields

### ARTICLE II

SECTION 1 The Association shall be governed by a Council which shall consist of the Officers of the Association, four Councillors, and a representative of the Board of Editors of the Journal of Immunology

SECTION 2 The Officers of the Association shall be a President, a Vice President, a Secretary, and a Treasurer

SECTION 3 The President, the Secretary, and the Treasurer shall be elected at the regular annual meeting of the Association to serve for one year. They shall take office the day after the end of the annual meeting

SECTION 4 The President shall not serve for more than one year consecutively. The Secretary and the Treasurer are eligible for reelection

SECTION 5 The outgoing President shall serve as Vice President for the year subsequent to his Presidency

SECTION 6 The Editors of the Journal of Im-

munology shall designate annually one out of their number as their representative with power to vote in the Council of the Association

SECTION 7 One Councillor shall be elected each year to serve for four years. No Councillor may be reelected until one year after expiration of his term. He may, however, serve in any other elective office immediately after expiration of his term as Councillor

SECTION 8 The President shall appoint a Nominating Committee of three (or more) members not holding executive office in the Association and shall designate the Chairman. The Nominating Committee shall make at least one nomination for each of the offices. Nominations made by the Nominating Committee shall be transmitted to the Secretary at least six weeks before the annual meeting. The Secretary shall send to every member of the Association, at least (four) weeks before the annual meeting, a ballot containing the list of the nominees and spaces for such additional nominees as the members might wish to propose

SECTION 9 The members may vote by mail. Ballots sent by mail must be in the hands of the Secretary before the opening of the annual meeting. Alternatively, members may vote at the annual meeting. At the annual meeting the Secretary shall present to tellers appointed by the President, all ballots received by him

SECTION 10 A plurality of votes shall be sufficient for election

SECTION 11 It is the duty of the Council to conduct the business of the Association

SECTION 12 Should a vacancy occur in the Council other than by expiration of term of service, the Council may elect a member to fill the vacancy until the next regular meeting

SECTION 13 The Vice President shall substitute for the President when necessary. If a vacancy should occur in the offices of the Secretary or Treasurer the Council may elect a member to fill the vacancy for the unexpired portion of the term

SECTION 14 In case of equal division of votes, the President shall cast the decisive ballot

### ARTICLE III

SECTION 1 The Association shall consist of active members, members emeriti, and honorary members

SECTION 2 Any qualified person engaged in the study of problems related to the purpose of the Association shall be eligible to active membership

SECTION 3 Candidates for active membership shall be nominated by two members of the Association on blanks furnished by the Secretary. Applications must be accompanied by letters of recommendation of the sponsors, a curriculum vitae, reprints of publication and other suitable evidence

of fitness. Nominations are to be submitted to the Council which shall determine eligibility and shall post a list of candidates at the annual meeting. The membership shall elect new members by majority vote.

SECTION 4 Failure to pay dues for three successive years shall annul membership. However, the Council may reinstate a member if an acceptable explanation is submitted.

SECTION 5 If a 2/3 majority of the Council decides that the interests of the Society require the expulsion of a member, the Secretary shall notify the affected member in writing of the charges. The Council shall allow a reasonable time for the presentation of his defence before voting. Upon recommendation of a 2/3 majority of the Council, the Secretary shall send a notice of the decision to each active member at least three weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion, and on a two thirds vote of the members present, the member shall be expelled, his assessment for the current year shall be returned and he shall cease to be a member of the Society.

SECTION 6 A member on attaining the age of sixty five years may elect to accept the status of member emeritus. As such he shall retain voting privileges but shall be relieved of all financial obligations to the Association including subscription to the Journal of Immunology and the Federation Proceedings.

SECTION 7 The Council may nominate for honorary membership persons of extraordinary achievement in the field of endeavor of this Association. Election to honorary membership shall follow the same procedure as that for election for office in the Association, and the Secretary, on order of the Council shall place nominations for honorary membership on the annual ballot.

#### ARTICLE IV

SECTION 1 The members present at the annual meeting of the Association shall constitute a quorum.

SECTION 2 A quorum of the Council for the transaction of all business shall be three.

#### BY-LAWS

1 A regular meeting of the Association shall be held annually at such time and place as the Council shall determine.

2 Special meetings of the Association may be held at the discretion of the Council.

3 Regular and special meetings shall be open to all members of the Association.

4 A meeting of the Council shall be held before each annual session of the Association.

5 The Past Presidents shall have the right of attending, without vote, the meetings of the Council.

6 The President may appoint a Past President *pro tempore* Counsellor at any stated meeting of the Council at which a quorum is not present.

7 The Council may transact, and vote by mail on, such business as cannot be conveniently transacted at meetings.

8 The fiscal year of the Association shall begin April first.

9 The Secretary shall arrange the program for the scientific meetings, with the advice of the other officers of the Association. Papers intended for presentation at the meetings shall conform to the standards of the Journal of Immunology. In case of doubt, the Secretary shall have the right to submit papers to the scrutiny of two members of the Editorial Board of the Journal of Immunology, whose decision shall be final.

10 The dues of the Association shall be determined annually by the Council and shall include subscription to the Journal of Immunology.

11 Proposed changes in the Constitution and By-Laws must be submitted in writing to the Secretary. The President shall then appoint a Committee of at least three members which shall communicate its recommendations to the Secretary.

12 Recommendations of such Committees shall be sent to the membership of the Association by the Secretary with the annual ballot. A change in the Constitution and the By Laws shall require a two thirds majority of the members casting votes either by mail or at the annual meeting.

13 The Journal of Immunology, which is the property and official organ of this Association, shall be administered for the Association by an Editorial Staff.

14 The Editorial Staff shall be organized and its members shall be elected by or may be removed by a majority vote of the Council of the Association.

15 If by force of circumstances it should be impossible to have an annual meeting, election of Officers and Council may be held entirely by mail. If this also should prove to be impossible, the Council may direct the Officers to continue in their Offices until such time as elections can be held.

16 The Council shall adopt temporary rules for the transition period after the adoption of the amended Constitution.

## ALPHABETICAL LIST OF ALL MEMBERS OF THE SIX SOCIETIES

The parenthesis following each listed name gives the Society affiliation and year of election

- (1) The American Physiological Society
- (2) The American Society of Biological Chemists
- (3) The American Society for Pharmacology and Experimental Therapeutics
- (4) The American Society for Experimental Pathology
- (5) The American Institute of Nutrition
- (6) The American Association of Immunologists

## HONORARY MEMBERS

- Adrian, E D Dept of Physiology, Cambridge University, Cambridge, England (1, 1946)
- Castaneda, M Ruiz, M D Investigaciones Medicas, Hospital General, Mexico, D F *Director, Department of Medical Research* (6, 1942)
- Chopra, R N, M A, M D, Sc D (Cantab), F R C P (London) P I E School of Tropical Medicine, Calcutta, India *Director, Professor of Pharmacology* (3, 1938)
- Dale, H H The Wellcome Trustees, Dilke House, Malet St, London, W C, England (3, 1926)
- Hektoen, Ludvig, M D 629 S Wood St, Chicago, Ill *President, Chicago Tumor Institute* (6, 1919)
- Hitchens, Arthur P, M D Public Building, Wilmington 33, Del *Health Commissioner, Wilmington, Del* (6, 1913)
- Houssay, Bernardo A, M D Viamonte 2790, Buenos Aires, Argentina *Director, and Professor of Physiology* (1, 1942)
- Huntoon, F M, M D Woodbridge, Conn (6, 1918)
- Krogh, August Juliane Marariesvej 34, Copenhagen, Denmark (1, 1946)
- Lapicque, L Laboratory of Physiology, The Sorbonne, Paris, France (1, 1946)
- Loewi, Otto, M D New York University College of Medicine, 477 First Ave, New York City *Research Professor in Pharmacology* (3, 1941)
- McCoy, George Walter, M D Louisiana State University Medical School, New Orleans *Director, Department of Public Health* (6, 1916)
- Novy, Frederick G, M D, Sc D, LL D 721 Forest Ave, Ann Arbor, Mich *Dean Emeritus and Professor Emeritus of Bacteriology, Medical School, University of Michigan* (6, 1920)
- Orbeli, L A Academy of Sciences of the USSR, Moscow, USSR (1, 1946)
- Sherrington, Sir Charles S, O M, Sc D, M D, F R S "Broomside," Valley Road, Ipswich, England *Former Waynefleete Professor of Physiology, Oxford University, Former President of the Royal Society* (1, 1904)

Sordelli, A Institute of Bacteriology, Department of Public Health, Buenos Aires, Argentina *Director* (6, 1942)

## MEMBERS

- Abramson, David I, M D Department of Medicine, University of Illinois, Chicago 12 *Assistant Clinical Professor, Attending Physician, Hines Veterans Hospital, Associate Physician, Michael Reese Hospital* (1, 1937)
- Abramson, Harold A, M D 133 E 58th St, New York City *Assistant Professor of Physiology, College of Physicians and Surgeons, Columbia University* (1, 1930, 2, 1934)
- Abreu, Benedict E, M S, Ph D, Division of Pharmacology, Univ of California Medical School, San Francisco *Assistant Professor of Pharmacology* (3, 1941)
- Acheson, George H, M D Harvard Medical School, 25 Shattuck St, Boston, Mass *Associate in Pharmacology* (1, 1942, 3, 1945)
- Adams, Georgian, M A, D Sc United States Department of Agriculture, Washington 25, D C *Senior Experiment Station Administrator, Office of Experiment Stations* (5, 1946)
- Adams, John M, M D Department of Pediatrics, W 205 University Hospital, University of Minnesota, Minneapolis *Associate Professor of Pediatrics* (4, 1947)
- Adams, Mildred, M A, Ph D Takamine Laboratory, Clifton, N J *Research Chemist* (2, 1934)
- Adams, R Charles, M D, C M, M S (Anesthesiology), Mayo Clinic, Rochester, Minn *Instructor in Anesthesia, Mayo Foundation, University of Minnesota Member of Mayo Clinic Staff, Section on Anesthesia* (3, 1942)
- Adams, W Lloyd, M D, Ph D, 134 Tamarack Rd, Stapleton 4, N Y U S Public Health Service, Staten Island, N Y (3, 1942)
- Adams, Wright R, B S, M D Dept of Medicine, University of Chicago, Chicago 37, Ill *Associate Professor of Medicine* (1, 1946)
- Addis, Thomas, M D, M R C P Lane Hospital,

- San Francisco, Calif *Professor of Medicine, Stanford University* (1, 1922)
- Addison, William H F, M D *School of Medicine, University of Pennsylvania, Philadelphia Professor of Histology and Embryology* (1, 1928)
- Ades, Harlow Whiting, Ph D *Box 731, Emory University, Ga* (1, 1915)
- Adler, Harry F, M S, Ph D, M D *Chief, Dept of Physiology, School of Aviation Medicine, Randolph Field, Texas* (1, 1913)
- Adolph, Edward Frederick, Ph D *School of Medicine and Dentistry, University of Rochester, Rochester, N Y Associate Professor of Physiology* (1, 1921)
- Adolph, William H, Ph D *Yenching University, Peiping, China Professor of Biochemistry* (2, 1916, 5, 1934)
- Ahlquist, Raymond P, M S, Ph D *Dept of Pharmacology, Univ of Georgia School of Medicine, Augusta Associate Professor of Pharmacology* (3, 1945)
- Albanese, Anthony A, Ph D *G 7 Tower Lab, Children's Medical Service, Bellevue Hospital, New York, N Y Assistant Professor of Pediatric Biochemistry, New York University College of Medicine* (2, 1944)
- Albaum, Harry G, A B, M Sc, Ph D *Brooklyn College, Bedford Avenue and Avenue H, Brooklyn, N Y Assistant Professor of Biology* (2, 1947)
- Albert, A, M A, Ph D, M D *Mayo Foundation, Rochester, Minn Research Associate* (1, 1947)
- Albritton, Errett C, M D *George Washington University Medical School, 1339 H St, N W, Washington, D C Professor of Physiology and Head of the Department of Physiology* (1, 1933)
- Alexander, Robert S, A B, M A, Ph D *School of Medicine, Western Reserve Univ, 2109 Adelbert Road, Cleveland, Ohio Instructor in Physiology* (1, 1946)
- Algire, Glenn H, M D *National Cancer Institute, Bethesda, Md Senior Assistant Surgeon, U S Public Health Service* (1, 1945)
- Allan, Frank N, M D *Lahey Clinic, 605 Commonwealth Ave, Boston, Mass Co director of the Medical Department* (4, 1930)
- Allen, Charles Robert, Ph D *University of Texas, School of Medicine, Galveston Assistant Professor of Department of Anesthesiology* (1, 1943)
- Allen, Frank W, Ph D *1557 Life Science Building, University of California, Berkeley, Calif Associate Professor* (2, 1947)
- Allen, Frederick M, M D *1031 Fifth Ave, New York City Professor of Medicine, Poly clinic Medical School and Hospital* (1, 1924, 4, prior to 1920)
- Allen, J Garrott, M D *University of Chicago, University Clinics, Chicago, Ill Instructor in Surgery* (1, 1943)
- Allen, Lane, M S, Ph D, M D *University of Georgia School of Medicine, University Place, Augusta Associate Professor of Anatomy* (1, 1939)
- Allen, Shannon C, Ph D *6914 Armour Drive, Oakland 11, Calif Pharmacology Laboratory, Western Regional Research Laboratory, Albany 6, Calif* (1, 1915)
- Allen, Thomas H, Ph D *College of Physicians and Surgeons, Columbia University, 630 168th St, New York 32, N Y Instructor in Physiology* (1, 1917)
- Allen, Willard M, M D *Washington University School of Medicine, 630 S Kingshighway Blvd, St Louis, Mo Professor of Obstetrics and Gynecology* (1, 1934)
- Allen, William F, Ph D, D Sc *University of Oregon Medical School, Portland Professor Emeritus of Anatomy* (1, 1929)
- Alles, Gordon A, M S, Ph D *770 S Arroyo Parkway, Pasadena, Calif Lecturer in Pharmacology, University of California Medical School, San Francisco, and Research Associate in Biology, California Institute of Technology, Pasadena* (1, 1932, 3, 1941)
- Alling, Eric L, M D *School of Medicine and Dentistry, University of Rochester, Rochester 7 N Y Associate in Radiology* (1, 1947)
- Allison, James B, Ph D *Rutgers Univ, New Brunswick, New Jersey Director, Bureau of Biological Research* (2, 1946)
- Almquist, Herman J, Ph D F E Booth Co Laboratories, 1290 Powell St, Emeryville, Calif *Director of Research* (2, 1937, 5, 1937)
- Alvarez, Walter C, M D *Mayo Clinic, Rochester, Minn Professor of Medicine, Mayo Foundation* (1, 1917, 3, 1921)
- Alving, Alf Sven, M D *Billings Hospital, University of Chicago, 950 E 59th St, Chicago, Ill Associate Professor of Medicine* (1, 1939)
- Amberg, Samuel, M D *Mayo Clinic, Rochester, Minn Associate Professor of Pediatrics, Mayo Foundation* (1, 1903, 2, 1906, 3, 1909)
- Amberson, William R, Ph D *University of Maryland School of Medicine, Baltimore Professor of Physiology* (1, 1924)
- Ambrose, Anthony M, M S, Ph D *Western Regional Research Laboratory, 800 Buchanan St, Albany, Calif Pharmacologist, U S Department of Agriculture, Bureau of Agricultural Chemistry and Engineering* (3, 1937)
- Amoss, Harold L, M D M S, Dr P H, Sc D *68 Deerfield Drive, Greenwich, Conn* (4, 1922, 6, 1917)
- Andersch, Marie A, Ph D *University Hospital,*



- Baltimore, Md *Biochemist, University Hospital, Instructor in Medicine, University of Maryland* (2, 1940)
- Andersen, Dorothy H., M D Babies Hospital, Broadway and 167th St, New York City *Associate in Pathology, Columbia University* (4, 1935)
- Anderson, Evelyn M., M A, M D 7206 Blair Rd, N W, Washington 12, D C (1, 1934)
- Anderson, Hamilton H., M S, M D *Pharmacology Laboratory, Univ of California Medical School, San Francisco Professor of Pharmacology* (3, 1931)
- Anderson, Oscar Daniel, Ph D Dept of Psychology, Cornell University, Ithaca, N Y (1, 1939)
- Anderson, Rudolph J., Ph D Sterling Laboratory, Yale University, New Haven, Conn *Professor of Chemistry* (2, 1915)
- Anderson, W A D, M A, M D Marquette University School of Medicine, Milwaukee, Wis *Professor of Pathology and Bacteriology* (4, 1941)
- Anderson, William E., M A Eastern State Farmers' Exchange, Westbrook Farm, Rockville, Conn *Biochemist* (2, 1931, 5, 1933)
- Andervont, H B, Sc D National Cancer Institute, Bethesda, Md *Biologist, U S Public Health Service* (4, 1939)
- Andrews, James C., Ph D University of North Carolina, Chapel Hill *Professor of Biological Chemistry and Nutrition* (2, 1925)
- Andrus, E Cowles, M D 24 E Eager St, Baltimore 2, Md *Assistant Visiting Physician, Associate Professor of Medicine, Johns Hopkins University* (1, 1925)
- Anfinson, Christian B., Jr., M S, Ph D Medical Nobel Institute, Hantverkargatan 3, Stockholm, Sweden *Associate in Biological Chemistry, Harvard Medical School* (2, 1946)
- Angerer, Clifford, Ph D Ohio State University, Columbus *Associate Professor of Physiology* (1, 1943)
- Angevine, D Murray, M D Univ of Wisconsin Medical School, Madison, Wis *Professor of Pathology* (4, 1940)
- Ansbacher, Stefan, M S, D Sc 17 Locl Court, Rockville Centre, N Y (2, 1939)
- Anson, Mortimer L., Ph D Continental Foods, Inc, Hoboken, N J *Director of Chemical Research* (2, 1937)
- Apperly, Frank L., M A, D Sc, M D, F R C P Medical College of Virginia, Richmond *Professor of Pathology* (4, 1936)
- Archibald, Reginald M., M A, Ph D, M D School of Hygiene and Public Health, Johns Hopkins University, 615 N Wolfe Street, Baltimore 5, Md *Professor of Biochemistry* (2, 1947)
- Arkin, Aaron, M A, M D, Ph D Suite 2006, 25 E Washington St, Chicago, Ill *Rush Professor of Medicine, U of Ill Prof and Chairman, Dept of Medicine, Cook County Graduate School* (1, 1914, 3, 1919)
- Armstrong, Philip B., M D College of Medicine, Syracuse Univ, Syracuse 10, N Y *Professor of Anatomy* (1, 1915)
- Armstrong, W D, M S, M D, Ph D 17 Medical Sciences Bldg, University of Minnesota, Minneapolis *Professor and Head of Physiological Chemistry* (2, 1938)
- Arnold, Aaron, M S, Ph D Sterling Winthrop Research Institute, Rensselaer, N Y *Head of Nutritional Research Laboratory* (5, 1947)
- Arnold, Lloyd, A M, M D 1538 E 57th St, Chicago, Ill (4, 1930, 6, 1925)
- Arnow, L Earle, Ph D, M D Medical Research Division, Sharp and Dohme, Glenolden, Pa *Director of Research* (2, 1940)
- Aronson, Joseph D., M D Phipps Institute, University of Pennsylvania, Philadelphia 4 *Associate Professor of Bacteriology* (4, 1927, 6, 1925)
- Artom, Camillo, M D Bowman Gray School of Medicine, Winston-Salem, N C *Professor of Biochemistry* (2, 1944)
- Ascham, Leah, Ph D Kansas State College, Manhattan *Professor, School of Home Economics* (5, 1935)
- Asenjo, Conrado F., Ch E, M S, Ph D School of Tropical Medicine, San Juan, Puerto Rico *Associate Professor of Chemistry and Head of Department of Chemistry and Nutrition, School of Tropical Medicine of the University of Puerto Rico under the Auspices of Columbia University* (2, 1944)
- Ashburn, Llewellyn L., M D National Institute of Health, Bethesda 14, Md *Senior Surgeon, U S Public Health Service* (4, 1947)
- Ashby, Winifred M., Ph D 305 10th St, N E, Washington, D C *Senior Scientist, Federal Security Agency (St Elizabeth's Hospital)* (6, 1923)
- Ashman, Richard, M S, Ph D School of Medicine, Louisiana State University, New Orleans *Professor of Physiology* (1, 1925)
- Astwood, Edwin Bennet, M D, C M, Ph D Pratt Diagnostic Hospital, 30 Bennet St, Boston, Mass *Research Professor of Medicine at Tufts Medical School* (1, 1939)
- Atkin, Lawrence, Ph D Wallerstein Labs, 180 Madison Ave, New York 16, N Y *Research Chemist* (2, 1946, 5, 1946)
- Aub, Joseph C., M D Harvard Medical School, Boston 15, Mass *Professor of Research Medicine* (1, 1919, 5, 1933)
- Auer, John, M D 1402 S Grand Blvd, St Louis, Mo *Professor of Pharmacology and Director*

- of the Department, *St Louis University School of Medicine* (1, 1905, 3, 1908)
- Austin, J Harold, M D 711 Maloney Clinic, 30th and Spruce Sts, Philadelphia, Pa Director, *Pepper Laboratory* (2, 1922)
- Austin, Richard Sisson, M D Cincinnati General Hospital, University of Cincinnati, Cincinnati, O Professor of Pathology (1, 1927)
- Avery, O T, M D, Sc D, LL D Hospital of the Rockefeller Institute, 66th St and York Ave, New York City Member *Emeritus*, *Rockefeller Institute for Medical Research* (4, 1921, 6, 1920)
- Axtmayer, Joseph H, B S, A M, Ph D University of Puerto Rico, Rio Piedras, Puerto Rico Professor of Chemistry (3, 1935)
- Ayo, Corrado, M D 750 S State St, Elgin, Ill (6, 1944)
- Babkin, B P, M D, D Sc, F R S C McGill University, Montreal, Canada Professor of Physiology (1, 1924)
- Bachem, Albert, Ph D College of Medicine, University of Illinois, 1853 W Polk St, Chicago Professor of Biophysics (1, 1933)
- Bachman, Carl, M D Department of Obstetrics, University of Pennsylvania School of Medicine, Philadelphia (2, 1941)
- Bachmann, George, M S, M D, F A C P 1088 Lullwater Road, N E, Atlanta, Ga Professor Emeritus of Physiology, *Emory University School of Medicine* (1, 1912)
- Baer, Erich, Ph D Banting and Best Department of Medical Research, 100 College St, Toronto, Ontario, Canada Associate Professor (2, 1942)
- Baernstein, Harry D, M S, Ph D National Institute of Health, Bethesda, Md Senior Biochemist (2, 1934)
- Baetjer, Anna M, D Sc Johns Hopkins School of Hygiene and Public Health, 615 N Wolfe St, Baltimore 5, Md Assistant Professor of Physiological Hygiene (1, 1929)
- Bahrs, Alice M, M A, Ph D The Martha Washington Hotel, 10th and Montgomery Sts, Portland, Ore (1, 1933)
- Bailey, Cameron Vernon, M D, C M 303 E 20th St, New York City Clinical Professor of Medicine, *New York Post-Graduate Medical School, Columbia University* (2, 1920, 5, 1933)
- Bailey, Orville T M D Harvard Univ Medical School, 25 Shattuck St, Boston, Mass Assistant Professor in Pathology (4, 1939)
- Bailey, Percival, M D, Ph D Univ of Illinois College of Medicine, 1853 West Polk St, Chicago 12, Ill Professor of Neurology and Neurosurgery (1, 1941)
- Baifsell, George Alfred, A M, Ph D Yale University, Osborn Zoological Lab, 165 Prospect St, New Haven, Conn Professor of Biology (1, 1915)
- Baker, A B, M D University of Minnesota Medical School, 19 Millard Hall, Minneapolis Associate Professor and Director of *Neuropsychiatry and Neuropathology* (1, 1910)
- Baker, James A, M D New York State Veterinary College, Cornell University, Ithaca, N Y (4, 1917)
- Baker, Roger D, M D Medical College of Alabama, Birmingham 5 Professor of Pathology (4, 1939)
- Baldes, Edward J, A M, Ph D 127 Fifth Ave, S W, Rochester, Minn Assistant Professor of Physics, *Mayo Foundation, Graduate School, University of Minnesota* (1, 1930)
- Baldwin, Francis Marsh, A M, Ph D University of Southern California, Los Angeles Professor of Zoology and Director of *Experimental Marine Biology* (1, 1919)
- Bale, William F, Ph D University of Rochester, School of Medicine and Dentistry, Rochester, N Y Associate in Radiology (1, 1943)
- Ball, Eric G, M A, Ph D Harvard Medical School, Boston, Mass Professor of Biochemistry (2, 1934)
- Ball, Howard A, M D San Diego County General Hospital, N Front St, San Diego, Calif Pathologist, *San Diego County General and Paradise Valley Hospitals* (4, 1937)
- Balls, Arnold Kent, Ph D Enzyme Research Laboratory, U S Bureau of Agricultural and Industrial Chemistry, Western Regional Research Laboratory, 800 Buchanan St, Albany 6, Calif Head Chemist, Adjunct Professor, *The George Washington University* (on leave) (2, 1932)
- Bang, Frederick B, M D Johns Hopkins Hospital, Baltimore, Maryland Assistant Professor in Medicine (4, 1947)
- Banus, Mario Garcia, M Sc, D Sc Bright Meadows, Chestertown, Md (1, 1927)
- Bard, Philip, A M, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore, Md Professor of Physiology, Member *National Academy of Sciences* (1, 1929)
- Barker, H A, Ph D 3048 Life Science Bldg, Univ of California, Berkeley 4, Calif Professor of Soil Microbiology (2, 1946)
- Barker, S B, Ph D College of Medicine, State University of Iowa, Iowa City Associate Professor of Physiology (1, 1938)
- Barlow, Orpheus W, M D, Ph D R F D 3 Warwick Road, Winchester, N H (1, 1936, 3, 1944)
- Barnes, B O, A M, Ph D Box 967, Station Hospital, KAAF, Kingman, Ariz Professor of Health Education, *University of Denver* (1, 1932)

- Barnes, LaVerne A, B S, M S, Ph D Naval Medical Research Institute, National Naval Medical Center, Bethesda 14, Maryland *Head, Bacteriology Facility* (6, 1931)
- Barnes, Richard Henry, Ph D Sharp & Dohme, Glenolden, Pa *Director of Biochemical Research, Medical Research Division* (2, 1941, 5, 1944)
- Barnes, Thomas C, D Sc Hahnemann Medical College, Philadelphia, Penna *Associate Professor of Physiology* (1, 1942)
- Barnum, Cyrus P, Jr, Ph D 210 Millard Hall, Univ of Minnesota, Minneapolis 14, Minn *Associate Professor of Physiological Chemistry* (2, 1946)
- Barott, Herbert G, E E U S Department of Agriculture, National Agricultural Research Center, Beltsville, Md *Biophysicist, Animal Nutrition Division, Bureau of Animal Industry* (5, 1938)
- Barrera, S Eugene, M D Albany Medical College, New Scotland Ave, Albany, N Y (1, 1937)
- Barron, Donald H, M S, Ph D, M A (Cambridge) Yale University School of Medicine, New Haven, Conn *Associate Professor of Physiology* (1, 1943)
- Barron, E S Guzman, M D Dept of Medicine, Univ of Chicago, Chicago 37, Ill *Associate Professor of Biochemistry* (2, 1931)
- Bartley, S Howard, Ph D P O Box 763, East Lansing, Mich (1, 1935)
- Bass, Allan D, M S, M D Univ of Syracuse School of Medicine, Syracuse, N Y *Professor of Pharmacology* (3, 1944)
- Batchelder, Esther L, A M, Ph D 8433 Woodcliff Ct, Silver Spring, Md (5, 1933)
- Bateman, John B, Ph D Physical & Chem Division, Camp Detrick, Frederick, Md (1, 1945)
- Bates, Robert W, Ph D E R Squibb and Sons, Biological Laboratories, New Brunswick, N J *Head, Endocrine Products Dept* (2, 1936)
- Batterman, Robert C, M D New York University College of Medicine, 477 First Ave, New York City *Instructor in Therapeutics* (3, 1941)
- Baudisch, Oskar, Ph D Saratoga Springs, N Y *Director of Research, Saratoga Springs Authority, State of New York* (4, 1931)
- Bauer, J H, M D The Rockefeller Foundation, 20 Rue de la Baume, Paris, (8<sup>e</sup>) France (4, 1935)
- Bauer, Walter, M D Massachusetts General Hospital, Boston *Associate Professor and Tutor in Medicine, Harvard Medical School, Colonel, MC, Army Service Forces Hq 8th Service Command, Dallas, Texas* (1, 1929)
- Bauernfeind, J C, M S, Ph D Hoffmann-La Roche, Inc, Nutley 10, N J *Chief of Applied Nutrition* (5, 1917)
- Bauman, Louis, M D Presbyterian Hospital, New York City *Assistant Professor of Clinical Medicine, Columbia University* (2, 1912)
- Baumann, Carl A, M S, Ph D Biochemistry Dept, University of Wisconsin, Madison *Professor of Biochemistry* (2, 1938, 5, 1938)
- Baumann, Emil J, Ph D 7 Church Lane, Scarsdale, N Y *Chemist, Montefiore Hospital* (2, 1922)
- Baumberger, J Percy, M S, Sc D Physiology Department, Stanford University, Calif *Professor of Physiology* (1, 1921)
- Baxter, James G, Ph D 228 Sagamore Drive, Rochester 12, N Y *Supervisor, Organic Research Dept, Distillation Products, Inc* (2, 1946)
- Bayne-Jones, Stanhope, M A, Sc D, M D New York Hospital, Cornell Medical Center, 525 E 68th St, New York 21, N Y *President, Joint Administrative Board* (1, 1927, 6, 1917)
- Bazett, Henry C, M A, M D, F R C S University of Pennsylvania, School of Medicine, Philadelphia *Professor of Physiology* (1, 1921)
- Beach, Eliot F, Ph D 660 Frederick St, Detroit 2, Mich *Assistant Director, Research Laboratory, Children's Fund of Michigan* (2, 1941, 5, 1942)
- Beadle, Buell W, M S, Ph D American West Institute, University of Chicago, 5757 Drexel Avenue, Chicago 37, Ill *Research Chemist* (2, 1917)
- Bean, John W, M S, Ph D, M D University of Michigan, Ann Arbor *Professor of Physiology* (1, 1932)
- Beard, Howard H, M A, Ph D Chicago Medical School, 710 S Wolcott Ave, Chicago, Ill *Professor of Biological Chemistry* (2, 1928, 5, 1933)
- Beard, Joseph W, M D Duke Hospital, Durham, N C *Professor of Surgery* (4, 1938, 6, 1940)
- Beazell, James Myler, Ph D, M D 104 South Michigan Ave, Chicago, Ill *Instructor in Physiology and Pharmacology, Northwestern Univ School of Medicine* (1, 1939)
- Beck, Claude S, M D Lakeside Hospital, Cleveland, O *Professor of Neurosurgery, Western Reserve University, Associate Surgeon, Lakeside Hospital* (4, 1930)
- Beck, Lyle V, M S, Ph D 9503 Edgley Road, Bethesda, Md (1, 1941)
- Becker, R Frederick, M S, Ph D Dept of Anatomy, Univ of Washington, Seattle 5, Wash (1, 1941)
- Becker, Theodore J, M A, Ph D Sterling Winthrop Research Institute, 33 Riverside Avenue, Rensselaer, N Y *Head, Pharmacology Section* (3, 1944)
- Beckman, Harry, M D Marquette University School of Medicine, Milwaukee, Wis *Profes-*

- sor and *Director of the Department of Pharmacology* (3, 1937)  
 Beecher, Henry K, M D Massachusetts General Hospital, Boston *Dorr Professor of Research in Anesthesia, Harvard Medical School, Ines-thetist in Chief, Massachusetts General Hospital* (3, 1940)  
 Behnke, Albert R, M S, M D Naval Medical Research Institute, Bethesda, Md *Executive Director* (1, 1916)  
 Behre, Jeanette Allen, Ph D Department of Biochemistry, College of Physicians and Sur-gons, 630 W 168th St, New York City *Associ-ate* (2, 1925)  
 Belding, David L, M D Boston University School of Medicine, Boston, Mass *Professor of Bacteriology and Experimental Pathology* (1, 1927)  
 Belding, Harwood S, Ph D QMC Climatic Laboratory, Lawrence, Miss *Director* (1, 1945)  
 Bell, E T, M D 110 Anatomy Bldg, University of Minnesota, Minneapolis *Professor of Path-ology* (4, 1931)  
 Bender, M B, M D New York University College of Medicine *Associate Professor of Neurology and Head of the Laboratory of Experi-mental Medicine* (1, 1947)  
 Benedict, Francis Gano, Ph D, Sc D, M D Machiasport, Me *Member of the National Academy of Sciences* (1, 1904, 2, 1906)  
 Benditt, Earl P, M D Department of Pathology, University of Chicago Clinics, Chicago 37, Ill *Instructor* (4, 1917)  
 Benham, Olive Ray, BS Connecticut State Department of Health, Bureau of Laboratories, Hartford *Chief Serologist* (6, 1941)  
 Bennett, A Lawrence, Ph D, M D College of Medicine, University of Nebraska, Omaha *Professor of Physiology and Pharmacology* (1, 1941)  
 Bennett, Granville A, M D University of Illinois College of Medicine, 1853 West Polk Street, Chicago *Professor of Pathology* (4, 1931)  
 Bennett, Henry S, M D Mass Institute of Tech-nology, Cambridge 30, Mass *Assistant Professor of Cytology* (1, 1946)  
 Bennett, Leslie L, M D University of Cali-fornia, Berkeley 4 *Assistant Professor of Physiology* (1, 1945)  
 Bennett, Mary Adeha, M A, Ph D Lankenau Hospital Research Institute, Philadelphia, Pa *Research Biochemist* (2, 1941)  
 Benson, Clara C, Ph D 160 Dorset St, West, Port Hope, Ontario, Canada *Professor Emeri-tus of Food Chemistry, University of Toronto* (2, 1906)  
 Berg, Benjamin N, M D 630 W 168th St, New York City *Associate in Pathology, Columbia University, College of Physicians and Surgeons* (1, 1928)  
 Berg, Clarence P, M A, Ph D Chemistry De-partment, State University of Iowa, Iowa City *Professor of Biochemistry* (2, 1933, 5, 1936)  
 Berg, William N, Ph D 225 W 106th St, New York City *Biochemist* (2, 1906)  
 Bergem, Olaf, M S, Ph D 1853 W Polk St, Chicago, Ill *Associate Professor of Physiologi-cal Chemistry, University of Illinois College of Medicine* (1, 1916, 2, 1911, 5, 1933)  
 Bergmann, Werner, Ph D Sterling Chemistry Building, Yale University, New Haven, Conn *Professor of Chemistry* (2, 1911)  
 Berkson, Joseph, M A, M D, D Sc Mayo Clinic, Rochester, Minn (1, 1933)  
 Bernard, Richard, M Sc, Ph D Department of Biology, Laval University, Blvd de l'Entente, Quebec, Canada *Assistant Professor of Physi-ology* (1, 1947)  
 Bernheim, Frederick, Ph D Box 3109, Duke Medical School, Durham, N C *Associate Pro-fessor of Physiology and Pharmacology* (2, 1933, 3, 1935)  
 Bernthal, Theodor G, M S, M D Dept of Physiology, Medical College, State of South Carolina, Charleston 16, S C *Professor of Physiology* (1, 1932)  
 Berry, George Packer, M D University of Rochester, Rochester, N Y *Assistant Dean, Professor of Bacteriology, Associate Professor of Medicine* (1, 1938, 6, 1934)  
 Bessey, Otto A, Ph D Public Health Research Institute of the City of New York, Inc, Foot of E 15th St, New York City *Member of the Institute, Chief of the Division of Nutrition and Physiology* (2, 1938, 5, 1943)  
 Best Charles Herbert, C B E, M A, M D, D Sc (London), D Sc (Chicago), F R S, F R C P (e), University of Toronto, Toronto, Ont, Canada *Director, Banting and Best Department of Medi-cal Research and Department of Physiology* (1, 1923, 2, 1923)  
 Bethell, Frank H, M D 409 Lenawee Drive, Ann Arbor, Mich *Associate Professor of Inter-nal Medicine and Assistant Director of the Thomas Henry Simpson Memorial Institute* (4, 1936)  
 Bethke, Roland M, M S, Ph D Ohio Agricul-tural Experiment Station, Wooster *In Charge of Nutritional Investigations* (2, 1928, 5, 1933)  
 Beutner, R, M D, Ph D 235 N 15th St, Philadelphia, Pa *Professor and Head of De-partment of Pharmacology, Hahnemann Medical College* (1, 1924, 3, 1924)  
 Beyer, Karl H, Ph D, M D Medical-Research Division, Sharp and Dohme, Inc, P O Box 7259, Glenolden, Pa *Director of Pharmacological Research* (1, 1942, 3, 1944)

- Bier, Otto, M D Instituto Postal 119-1, Sao Paulo, Brazil (6, 1947)
- Biefer, Raymond N, M D, Ph D University of Minnesota, Minneapolis *Professor of Pharmacology* (3, 1930)
- Bills, Charles E, M A, Ph D Mead Johnson & Co, Evansville, Ind *Director of Research* (2, 1928, 5, 1935)
- Bing, Franklin C, Ph D 1135 Fullerton Ave, Chicago, Ill *Director, American Institute of Baking, Assistant Professor of Physiology, Northwestern University Medical School* (2, 1931, 5, 1934)
- Bing, Richard J, M D Department of Surgery, Johns Hopkins Hospital, Baltimore 5, Md *Assistant Professor of Surgery* (1, 1912)
- Binger, Carl A, M D 125 E 73rd St, New York City *Assistant Professor of Clinical Medicine (Psychiatry), Cornell University Medical College* (1, 1927)
- Binkley, Francis, M S, Ph D School of Medicine, University of Utah, Salt Lake City, Utah *Associate Professor* (2, 1947)
- Binkley, Stephen Bennett, M S, Ph D Bristol Laboratories, Inc, Syracuse, N Y *Assistant Director of Research* (2, 1911)
- Bird, Herbert R, M S, Ph D Bureau of Animal Industry, Agricultural Research Center, Beltsville, Md *Senior Biochemist* (5, 1947)
- Bird, Orson D, M S, Ph D Research Laboratories, Parke, Davis and Co, Detroit 32, Mich *Research Biochemist* (2, 1947)
- Bisbey, Bertha, A M, Ph D Gwynn Hall, University of Missouri, Columbia *Professor of Nutrition* (5, 1933)
- Bischoff, Fritz E, M S, Ph D Cottage Hospital, Santa Barbara, Calif *Director of Research* (2, 1928, 5, 1933)
- Bishop, George H, Ph D Washington University Medical School, Euclid and Kingshighway, St Louis, Mo *Professor of Bio-Physics* (1, 1923)
- Biskind, Gerson R, M D Mt Zion Hospital, San Francisco, Calif *Pathologist, Mt Zion Hospital, Clinical Instructor in Pathology, University of California Medical School* (4, 1944)
- Black, Alex, M S, Ph D Department of Animal Nutrition, Pennsylvania State College, State College, Penn *Professor of Animal Nutrition* (5, 1947)
- Black, Edgar C, Ph D Department of Biology and Botany, University of British Columbia, Vancouver, B C, Canada (1, 1943)
- Blair, Edgar A, M S, Ph D Armored Medical Research Laboratory, Fort Knox, Ky *Lt Col* (1, 1936)
- Blair, Henry A, M Sc, Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Associate Professor of Physiology* (1, 1934)
- Blake, Francis G, M D, M A (hon), Sc D Yale University School of Medicine, New Haven, Conn *Sterling Professor of Medicine* (4, prior to 1920, 6, 1921)
- Blanchard Ernest W, Ph B, M S, Ph D Schieffelin and Co, 30 Cooper Sq, New York 3, N Y *Director of Research* (1, 1946)
- Blankenhorn, M A, M D University of Cincinnati, Cincinnati, O *Professor of Medicine* (4, 1932)
- Blatherwick, Norman R, M S, Ph D, Sc D Metropolitan Life Ins Co, 1 Madison Ave, New York City *Director of Biochemical Laboratory* (1, 1915, 2, 1915, 5, 1934)
- Blau, Nathan F, Ph D, Dept of Chemistry, University of Notre Dame, Notre Dame, Indiana *Research Associate in Organic Chemistry* (2, 1928)
- Blish, Morris J, M A, Ph D Amino Products Company, Rossford, O *Research Director* (2, 1944)
- Bliss, Alfred, M A, Ph D Tufts College Medical School, Boston, Mass *Assistant Professor of Physiology* (1, 1947)
- Bliss, Chester Ittner, Ph D Conn Agr Expt Sta, P O Box 1106, New Haven *Biometrician, Lecturer in Biometry, Yale University* (3, 1944)
- Bliss, Eleanor A, Sc D Department of Preventive Medicine, Johns Hopkins Hospital, 615 N Wolfe St, Baltimore, Md *Associate in Preventive Medicine, Johns Hopkins University School of Medicine* (6, 1931)
- Bloch, Konrad, Ph D Department of Biochemistry, University of Chicago, Chicago, Illinois *Assistant Professor of Biochemistry* (2, 1944)
- Block, Richard J, Ph D 15 Cooper Rd, Scarsdale, N Y *Director of Research, C M Armstrong Co, Associate, Department of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospital* (2, 1934, 5, 1933)
- Block, Walter D, M S, Ph D University Hospital, Ann Arbor, Mich *Assistant Professor of Biological Chemistry, University of Michigan Medical School* (2, 1942)
- Bloom, William, M D 1419 E 56th St, Chicago, Ill *Professor of Anatomy, University of Chicago* (4, 1930)
- Bloomfield, A L, M D Stanford University Hospital, San Francisco, Calif *Professor of Medicine* (3, 1927, 4, 1927)
- Bloor, W R, A M, Ph D, LL D School of Medicine and Dentistry, University of Rochester, Rochester, N Y *Professor of Biochemistry* (1, 1915, 2, 1910)
- Blum, Harold F, Ph D Department of Biology, Princeton University, Princeton, N J *Physi-*

- ologist, National Cancer Institute, and Visiting Lecturer (1, 1928)
- Blumberg, Harold, Sc D Research Laboratories, Indo Products, Inc 10 101st St, Richmond Hill 18, N Y (5, 1912)
- Blumenstock, Julius, M D Room D 127, Hines Unit, Hines, Ill (1, 1925)
- Blumgart, Hermann L, M D Beth Israel Hospital, 330 Brookline Ave, Boston, Mass Associate Professor of Medicine, Harvard Medical School, 11 Col MC (1, 1927)
- Blunt, Katharine, Ph D, LL D 38 Glenwood Ave, New London, Conn President Emeritus, Connecticut College for Women (2, 1921)
- Bock, Joseph C, Ch E, Ph D 2321 N 16th St, Milwaukee 10, Wis Professor Emeritus of Biochemistry, Marquette Univ Medical School, Biochemist, Milwaukee County Hospital (2, 1916)
- Bodansky, Aaron, Ph D Hospital for Joint Diseases, 1919 Madison Ave, New York City Biological Chemist (2, 1926)
- Bodansky, Oscar, Ph D, M D 1300 York Ave, New York 21 N Y Research Associate in Pharmacology, Cornell University Medical College, Lecturer in Pediatrics, New York University Medical College, Post Graduate Div (2, 1937, 3, 1942)
- Bodine, Joseph Hall, Ph D State University of Iowa, Iowa City Professor and Head of Department of Zoology (1, 1925)
- Boell, Edgar J, Ph D Osborn Zoological Laboratory, Yale University, New Haven, Conn Ross G Harrison Professor of Experimental Zoology (1, 1912)
- Bogert, L Jean, Ph D Hotel Claremont, Berkeley, Calif (2, 1917)
- Bogert, Marston Taylor, Sc D, LL D, R N D 116 S Fifth Ave New York 29, N Y Apt 14B Professor Emeritus of Organic Chemistry, Columbia University, Member, National Academy of Sciences (2, 1925)
- Bolliger, Adolph, Ph D Gordon Craig Research Laboratories, University of Sydney, Sydney, Australia Director of Research (2, 1928)
- Bollman, J L, M D Mayo Clinic, Rochester, Minn Associate in Division of Experimental Surgery and Pathology, Mayo Clinic, Professor of Physiology, Mayo Foundation, University of Minnesota (4, 1927)
- Bond, Glenn C, Ph D, M D The Upjohn Co, Research Laboratories, Kalamazoo, Mich Assistant Dept Head, Bacteriology Research (6, 1939)
- Bonnycastle, Desmond D, M D, Ph D Yale School of Medicine, 333 Cedar Street, New Haven, Conn Assistant Professor of Pharmacology (3, 1947)
- Bonsnes, Roy W, B S, Ph D Department of Biochemistry, Cornell University Medical College, 1300 York Ave, New York 21, N Y Associate Professor of Biochemistry in Obstetrics (2, 1917)
- Booher, Lela E, Ph D General Mills, Inc, Minneapolis, Minn Chief Nutritionist (2, 1933, 5, 1933)
- Bookman, Samuel, M A, Ph D 621 Madison Ave, New York City Consulting Chemist, Mt Sinai Hospital (2, 1912)
- Boor, Alden K, M S, Ph D Department of Medicine, University of Chicago, Chicago, Ill Research Associate (Associate Prof) of Biochemistry (2, 1931)
- Boothby, W M, M D, M A, F A C S, F A C P, Metabolism Laboratory, The Mayo Clinic, Rochester, Minn Chief of Section of Clinical Metabolism in Division of Medicine, Mayo Clinic, Professor of Experimental Metabolism, Mayo Foundation University of Minnesota Chairman, Mayo Aero Medical Unit, Member Subcommittee on Oxygen and Anoxia, V R C, O S R D (1, 1915, 2, 1920, 3, 1923, 4, 1924)
- Bordley, James, III, M D Mary Imogene Bassett Hospital, Cooperstown N Y (1, 1938)
- Borek, Ernest, Ph D College of the City of New York, Convent Avenue and 140 Street New York N Y Instructor in Chemistry College of the City of New York, Research Associate, Biochemistry, Columbia University (2, 1947)
- Boroff, Daniel A, M A, M S Camp Detrick, Frederick, Md Medical Bacteriologist, Project Chief (6, 1947)
- Borsook, Henry, M D, Ph D California Institute of Technology, Pasadena 4 Professor of Biochemistry (2 1931)
- Bosshardt, David K, M S Ph D Medical Research Division, Sharp and Dohme, Inc, Glenolden, Pennsylvania Research Biochemist (5, 1947)
- Bosworth, Alfred Willson, A M, M D R D 4, Circleville, O Consulting Chemist (2, 1936, 5, 1935)
- Bott, Phyllis A, M S Ph D Woman's Medical College of Pennsylvania Henry Ave and Abbot'sford Rd Philadelphia Associate Professor of Physiological Chemistry and Chairman of the Department (2, 1938)
- Boucher, Robert V, M A, Ph D 303 Frear Labs State College, Pa Professor of Agricultural and Biological Chemistry (5, 1945)
- Bouman, H D, M D University of Wisconsin Medical School, Madison Professor of Physical Medicine (1, 1943)
- Bourne, Wesley, M D, C M, M Sc, F R C P, D A (R C P & S, Eng) McGill University, Montreal, Canada Lecturer in Anesthetics, Dept of Pharmacology and Therapeutics (3, 1936)

- Bourquin, Helen, M S , Ph D 1331 N Tejon St , Colorado Springs, Colo (1, 1925)
- Bowman, Donald E , A M , Ph D 6956 Warwick Rd , Indianapolis, Ind Associate Professor of Biochemistry, Indiana University School of Medicine (2, 1944)
- Bowman, Katherine L , B A 20 Plaza Street, Brooklyn 17, N Y (6, 1946)
- Boxer, George E , Ph D 605 Girard Ave , Westfield, N J Senior Chemist, Research and Development Division, Merck & Co , Inc (2, 1946)
- Boyd, Eldon M , M A , M D , C M Queen's University, Kingston, Ontario, Canada Professor and Head of the Department of Pharmacology (3, 1941)
- Boyd, Milford J , M S , Ph D University of Cincinnati College of Medicine, Eden and Bethesda, Cincinnati 19, Ohio Assistant Professor (2, 1947)
- Boyd, T E , Ph D 12 Weyburn Road, Scarsdale, N Y (1, 1924)
- Boyd, William C , A M , Ph D Boston University School of Medicine, 80 E Concord St , Boston, Mass Associate Professor of Biochemistry (2, 1940, 6, 1933)
- Boyden, Edward A , A M , Ph D University of Minnesota, Minneapolis 14 Professor of Anatomy and Chairman of the Department (1, 1929)
- Boyer, Paul D , M S , Ph D Division of Biochemistry, College of Agriculture, University of Minnesota, St Paul 1 Associate Professor (2, 1944)
- Boyle, Paul E , D M D School of Dentistry, University of Pennsylvania, 40th and Spruce Sts , Philadelphia 4 Professor of Oral Pathology (4, 1939)
- Bozler, Emil, Ph D Ohio State University, Columbus Professor of Physiology (1, 1932)
- Bradbury, James T , M S , Sc D Dept of Obstetrics and Gynecology, University Hospitals, Iowa City Assistant Professor of Obstetrics and Gynecology (1, 1941)
- Bradley, Harold C , Ph D 2914 Oxford Rd , Madison 5, Wis Professor of Physiological Chemistry, University of Wisconsin (1, 1911, 2, 1908)
- Bradley, Stanley E , M D College of Physicians and Surgeons, 620 West 168th Street, New York 32, N Y Assistant Professor (1, 1947)
- Bradley, William B , Ph D American Institute of Baking, 1046 Elmwood Ave Wilmette, Ill Director of Laboratories (1, 1939)
- Branch, Charles F , M D The American College of Surgeons, 40 E Erie St , Chicago 11, Ill Assistant Director (4, 1940)
- Branch, E Arnold G , M D Bureau of Laboratories, General Hospital, St John, N B Director, Bureau of Laboratories, New Brunswick Department of Health (4, 1929)
- Brand, Erwin, Ph D 630 W 168th St , New York City Associate Professor of Biological Chemistry, Columbia University (2, 1929)
- Brandes, W W , M D Roosevelt Hospital, W 59th St , New York City (4, 1931)
- Branham, Sara E , Ph D , M D , Sc D National Institute of Health, Bethesda, Md Senior Bacteriologist (6, 1926)
- Branion, Hugh Douglas, M A , Ph D Ontario Agricultural College, Guelph, Canada Professor and Head of Dept of Animal Nutrition (5, 1933)
- Brassfield, Charles R , Ph D University of Michigan, Ann Arbor Associate Professor of Physiology (1, 1937)
- Bratton, Andrew Calvin, Jr , M D , Ph D Research Laboratories, Parke, Davis and Co , Detroit 32, Mich Director of Pharmacological Research (3, 1941)
- Braun, Herbert A , Ph D Food & Drug Administration, Federal Security Agency, Washington, D C Associate Pharmacologist (3, 1941)
- Brazier, Mary A B , Ph D Electroencephalographic Laboratory, Massachusetts General Hospital, Boston 14 Research Associate in Neuropathology, Harvard Medical School (1, 1947)
- Brewer, George, M D University of Louisville, Louisville, Ky (1, 1937)
- Bridge, Edward M , M D 219 Bryant St , Buffalo, N Y Research Professor, Department of Pediatrics, Univ of Buffalo (2, 1940)
- Briggs, A P , M D University of Georgia, Augusta Associate Professor in Biochemistry and Medicine (2, 1923)
- Briggs, David, R , M S , Ph D Division of Agricultural Biochemistry, University Farm, University of Minnesota, St Paul 8, Minn Professor of Agricultural Biochemistry, Chemist, Minn Agriculture Experiment Station (2, 1946)
- Briggs, George M , M S , Ph D Department of Poultry Husbandry, University of Maryland, College Park, Md Professor of Poultry Nutrition (5, 1947)
- Brink, Frank, Jr , Ph D Johnson Research Foundation, University of Pennsylvania, Philadelphia Fellow in Medical Physics, Johnson Research Foundation, Lecturer in Biophysics, Graduate School, University of Pennsylvania (1, 1942)
- Brinkhous, K M , M D Dept of Pathology, University of North Carolina School of Medicine, Chapel Hill, N C Professor of Pathology (4, 1939)
- Britton, Sydney W , M D University of Virginia School of Medicine, University Professor of Physiology (1, 1925)



- Brobeck, John R, M D, Ph D Yale University School of Medicine, New Haven, Conn Assistant Professor of Physiology (1, 1913)
- Brodie, Bernard B, Ph D New York University Research Service, Goldwater Memorial Hospital, New York City Research Associate in Biochemistry, Assistant Professor of Pharmacology, New York University Medical College (2, 1910, 3, 1915)
- Brody, Samuel, M A, Ph D Dairy Building, University of Missouri, Columbia Professor of Dairy Husbandry, College of Agriculture and Agricultural Experimentation (2, 1929, 5, 1933)
- Bronfenbrenner, J J, Ph D, D P H Washington University School of Medicine, St. Louis, Mo Professor of Bacteriology and Immunology (4, 1940, 6, 1918)
- Bronk, Detlev W, M S, Ph D, Sc D The Elbridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia Johnson Professor of Biophysics and Director, Johnson Foundation, Member National Academy of Sciences (1, 1927)
- Brookes, Margaret C Hessler, M A, Ph D University of Chicago, Chicago, Ill Assistant Professor, Department of Home Economics (5, 1935)
- Brookhart, John M, B A, M S, Ph D 1910 W Eddy St, Chicago 13, Illinois Assistant Professor, Physiology, Loyola Univ (1, 1916)
- Brooks, Chandler McCuskey, M A, Ph D Johns Hopkins University School of Medicine, Baltimore, Md Associate Professor of Physiology (1, 1934)
- Brooks, Clyde, Ph D, M D, LLD University Clinic, 2506 Ponce de Leon Blvd, Coral Gables, Fla (1, 1910, 3, 1912)
- Brooks, Matilda Moldenhauer, M S, Ph D Department of Zoology, University of California, Berkeley Research Associate in Biology (1, 1923)
- Brooks, Sumner Cushing, Ph D University of California, Berkeley Professor of Zoology (1, 1923)
- Brown, Goronwy Owen, M D 1325 S Grand Blvd, St. Louis, Mo Professor of Internal Medicine, St. Louis University (4, 1927)
- Brown, Claude P, M D Penn State Board of Health, Bureau of Laboratories, 34th and Locusts Sts, Philadelphia, Pa, Director (6, 1913)
- Brown, Dugald E S, M A, Ph D Bermuda Biological Station, St. George's W Bermuda (1, 1932)
- Brown, Edgar D, Pharm D, M D Paynesville, Minn Associate Professor of Pharmacology Emeritus (1, 1907, 3, 1909)
- Brown, Ethan Allan, L R C P (Eng), A R C S (London), 75 Bay State Rd, Boston, Mass Lecturer in Medicine, Tufts College Medical School, Physician in chief, Allergy Clinic, Boston Dispensary (6, 1916)
- Brown, Frank A, Jr, M A, Ph D Zoological Laboratories, Northwestern University, Evanston, Ill Associate Professor of Zoology (1, 1910)
- Brown, George B, M S, Ph D 800 Grove Street, Muncie, Ind Associate Member, Sloan-Kettering Institute for Cancer Research, Instructor in Biochemistry, Cornell University Medical College (2, 1947)
- Brown, John B, M S, Ph D Ohio State University, Columbus Professor of Physiological Chemistry (2, 1927, 5, 1931)
- Brown, R A, M S, Ph D, The Research Laboratories, Pirke Davis and Co, Detroit 32, Mich Head, Division of Nutritional Research (5, 1946)
- Brown, Rachel, M S, Ph D 26 Buckingham Drive, Albany, N Y Senior Biochemist, Division of Laboratories and Research, New York State Department of Health (6, 1933)
- Brown, Robert V, Ph D Department of Pharmacology University of Tennessee, Memphis 3 Associate Professor (1, 1945)
- Browne, J S L, M D, Ph D, F R S C University Clinic, Royal Victoria Hospital, Montreal, Canada Assistant Professor of Medicine, McGill University (1, 1934)
- Brownell, Katharine A, M A, Ph D Department of Physiology, Ohio State University, Columbus Research Associate (1, 1943)
- Brozek, Josef, Ph D Stadium South Tower, University of Minnesota, Minneapolis 14 Assistant Professor, Laboratory of Physiological Hygiene University of Minnesota School of Public Health (1, 1947)
- Brues, Austin M M D P O Box 5207, Chicago 80, Ill (1, 1940)
- Bruger, Maurice, M D, C M, M Sc 45 Gramercy Park N New York, N Y Associate Clinical Professor of Medicine, New York Post-Graduate Medical School of Columbia University, Chief, Division of Pathological Chemistry, New York Post Graduate Hospital (2, 1935, 5, 1935)
- Bruhn, John M, Ph D Department of Physiology, Medical College of Alabama 620 South 20th St Birmingham 5 Professor of Physiology and Pharmacology (1, 1939)
- Bruner, Harry Davis, M S, M D, Ph D University of North Carolina, Chapel Hill, N C Professor of Pharmacology (3, 1945)
- Brunschwig, Alexander, M D Cornell University Medical College New York City Professor of Clinical Surgery Attending Surgeon, Memorial Hospital (4, 1937)
- Bryan, W Ray Ph D Glen Rd, Rockville, Md Principal Biologist, National Cancer Institute (1, 1934, 4, 1940)

- Buchanan, J William**, Ph D Northwestern University, Evanston, Ill *Professor of Zoology* (1, 1927)
- Buchbinder, Leon**, Ph D Department of Health, 125 Worth St, New York City (6, 1934)
- Buchbinder, William C**, M S, M D 104 S Michigan Ave, Chicago, Ill *Assistant Professor of Medicine, Northwestern University Medical School, Associate in Medicine, Michael Reese Hospital* (1, 1940)
- Bucher, Gladys R**, M S, Ph D, Department of Biology, University of Illinois, Chicago Division, Navy Pier, Chicago 12 (1, 1946)
- Buckner, G Davis**, Ph D Kentucky Agricultural Experiment Station, Lexington *In Charge of Animal Nutrition* (2, 1920)
- Buey, Paul C**, M S, M D 4833 S Woodlawn Ave, Chicago, Ill *Professor of Neurology and Neurological Surgery, University of Illinois* (1, 1933)
- Buddingh, G John**, M D Vanderbilt University School of Medicine, Nashville, Tenn *Professor of Bacteriology* (4, 1940)
- Bueding, Ernest**, M D Dept of Pharmacology, Western Reserve Univ School of Medicine, Cleveland, Ohio *Assistant Professor* (2, 1916)
- Buell, Mary V**, Ph D 115 Ely Place, Madison 5, Wis (2, 1921)
- Bugher, John C**, M D Rockefeller Foundation, 49 W 49th St, New York 20 *Member of Staff International Health Division of the Rockefeller Foundation* (4, 1935)
- Bukantz, Samuel C**, M D Washington University School of Medicine, St Louis 10, Mo *Research Assistant in Medicine* (6, 1943)
- Bulatao, Emilio**, M D University of the Philippines, Manila, P I *Professor of Physiology and Biochemistry* (1, 1924)
- Bulger, Harold A**, Ph D, M D Barnes Hospital, 600 S Kingshighway, St Louis, Mo *Assistant Professor of Clinical Medicine, Washington University* (5, 1933)
- Bull, Henry B**, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Professor of Chemistry* (2, 1937)
- Bunde, Carl A**, M A, Ph D Southwestern Medical Foundation, Dallas, Texas *Associate Professor of Physiology and Pharmacology* (1, 1943)
- Bunney, William Edward**, Ph D E R Squibb and Sons, New Brunswick, N J *Vice-President—Director of Manufacturing Labs* (6, 1931)
- Bunting, Charles H**, M D 139 Armory St, Hamden, Conn *Emeritus Professor of Pathology, University of Wisconsin, Lecturer in Pathology, Yale Medical School* (4, 1913)
- Bunzell, H H**, Ph D Box 44, General Post Office, New York 1, N Y *Director, Bunzell Laboratories* (2, 1908)
- Burchell, Howard B**, M D, Ph D 102-110 2nd Ave, S W, Rochester, Minn *Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Consultant in Medicine, Mayo Clinic, Rochester, Minn* (1, 1942)
- Burdick, H O**, M A, Sc D (hon) Alfred University, Alfred, N Y *Professor of Biology* (1, 1940)
- Burdon, Kenneth L**, Sc M, Ph D Baylor University College of Medicine, Houston, Texas *Professor of Bacteriology, Consultant, United States Public Health Service* (6, 1936)
- Burge, W E**, A M, Ph D Indian River City, Fla (1, 1911)
- Burk, Dean**, Ph D National Cancer Institute, U S Public Health Service, Bethesda, Md *Senior Chemist* (2, 1939)
- Burns, Edward L**, M D Mercy Hospital, Toledo, Ohio *Pathologist* (4, 1939)
- Burr, George O**, M A, Ph D, LL D Experiment Station, H S P A, Honolulu, Hawaii, *Head, Dept of Biochemistry & Physiology* (2, 1928, 5, 1933)
- Burris, Robert H**, M S, Ph D Dept of Biochemistry, University of Wisconsin, Madison 6, Wis *Associate Professor of Biochemistry* (2, 1946)
- Burrows, Montrose T**, M D 5202 Maywood Ave, Los Angeles 41, Calif (4, prior to 1920)
- Burrows, William**, M S, Ph D Department of Bacteriology and Parasitology, University of Chicago, Chicago, 37, Ill *Professor of Bacteriology* (6, 1917)
- Burton, Alan C**, Ph D Department of Medical Research, University of Western Ontario, London, Canada *Assistant Professor of Medical Research* (1, 1937)
- Burton-Opitz, Russell**, M S, M D, Ph D 218 Bridle Way, Palisade, N J *Attending Cardiologist, Lenox Hill Hospital, Attending Physician, Cumberland Hospital, Consulting Cardiologist, Englewood, North Hudson, Holy Name and Hackensack Hospitals* (1, 1902, 2, 1906, 3, 1919)
- Buschke, William H**, M D Manhattan Eye, Ear and Throat Hospital, 210 East 64th St, New York 21, N Y *Research Ophthalmologist, Head, Ayer Foundation Ophthalmic Research Laboratory* (1, 1947)
- Bush, Milton T**, Ph D Vanderbilt University School of Medicine, Nashville, Tenn *Associate Professor of Pharmacology* (3, 1938)
- Butler, Thomas C**, M D Johns Hopkins School of Medicine, Dept of Pharmacology and Experimental Therapeutics, 710 N Washington St, Baltimore 5, Md *Associate Professor of Pharmacology and Experimental Therapeutics* (3, 1938)
- Butt, Hugh R**, M D Mayo Clinic, 102 Second Ave, S W, Rochester Minn *Consultant in Med*

- icine, Assistant Professor of Medicine, Mayo Foundation (5, 1912)
- Butts, Joseph S, M S, Ph D Oregon State College, Corvallis, Oregon Professor of Biochemistry and Head of Agricultural Chemistry (2, 1930, 5, 1946)
- Butz, Eleanor W J, Ph D Beltsville, Md Collaborator, Div Animal Husbandry, U S D A, Beltsville Research Center (6, 1935)
- Cahill, William M, Ph D Wayne County Laboratories, 431 Fischer Ave., Detroit 13, Mich Chemist Toxicologist (2, 1910)
- Cajori, Florian A, Ph D Dept of Biochemistry, Univ of Colorado Medical School, Denver 7, Colo Assistant Professor of Biochemistry (2, 1922, 5, 1933)
- Caldwell, Mary L, A M, Ph D Department of Chemistry, Columbia University, New York City Associate Professor of Chemistry (2, 1924, 5, 1933)
- Calloway, Nathaniel Oglesby, Ph D, M D Medical School, University of Illinois, 1819 Polk St, Chicago 12 Assistant in Medicine (3, 1945)
- Calvin, D Bailey, M A, Ph D University of Texas, Medical Branch, Galveston Professor, Biological Chemistry and Dean, Student and Curricular Affairs (1, 1934, 2, 1939)
- Cameron, A T, M A, D Sc, F I C, F R S C Medical College, Winnipeg, Manitoba, Canada Professor of Biochemistry, Faculty of Medicine, University of Manitoba, Biochemist, Winnipeg General Hospital (2, 1914)
- Camp, Walter J R, M D, Ph D 1853 Polk St, Chicago, Ill Professor of Pharmacology and Therapeutics, University of Illinois (3, 1926)
- Campbell, Berry, Ph D University of Minnesota, Minneapolis 14 Assistant Professor of Anatomy (1, 1945)
- Campbell, Dan H, M S, Ph D Department of Chemistry, California Institute of Technology, Pasadena, Calif Assistant Professor of Immunochemistry (6, 1938)
- Campbell, H Louise, Ph D 900 Windsor Ave, Windsor, Conn Retired (5, 1933)
- Campbell, James, M A, Ph D University of Toronto, Toronto, Ontario, Canada Assistant Professor of Physiology Lieutenant Commander, (S B) R C N V R (1, 1943)
- Campbell, Walter Ruggles, M A, M D, F R C P (C), F R S C 69 Madison Ave, Toronto, Canada Assistant Professor of Medicine and Clinical Medicine, University of Toronto, Assistant Physician, Toronto General Hospital (2, 1922)
- Cannan, R Keith, D Sc 477 First Ave, New York City Professor of Chemistry, New York University College of Medicine (2, 1931)
- Cannon, Paul R, M D, Ph D University of Chicago, Chicago, Ill Professor of Pathology (1, 1930, 6, 1929)
- Cantarow, Abraham, M D Jefferson Medical College, Philadelphia 7, Pa Professor of Physiological Chemistry (1, 1932, 3, 1935)
- Cantoni, G L, M D Long Island College of Medicine, 350 Henry St, Brooklyn 2, N Y Assistant Professor of Physiology and Pharmacology (3, 1915)
- Canzanelli, Attilio, M D Tufts College Medical School, 116 Huntington Ave, Boston, Mass Professor of Physiology (1, 1944)
- Carlson, A J, A M, Ph D, M D, LL D Hull Physiological Laboratory, University of Chicago, Chicago, Ill Professor of Physiology Emeritus, Member of the National Academy of Sciences (1, 1901, 5, 1933)
- Carlson, Foren D, Ph D Dept of Physiology and Biophysics, School of Medicine, Univ of Washington, Seattle 5 (1, 1945)
- Carmichael, Emmett B, Ph D Department of Biochemistry, The Medical College of Alabama, Birmingham 5 Professor of Biochemistry (1, 1931, 2, 1946)
- Carmichael, Leonard, Ph D, Sc D, Litt D, LL D Tufts College, Medford, Mass Director, the Tufts College Research Laboratory of Sensory Psychology and Physiology and President of the College (1, 1937)
- Carpenter, Thorne M, Ph D Sc D (hon) 27 Market St, Foxboro, Mass (1, 1915, 2, 1909, 5, 1935)
- Carr, C Jelleff, Ph D School of Medicine, University of Maryland, Baltimore Associate Professor of Pharmacology (3, 1940)
- Carr, Jesse L, M D University of California Medical School, Third and Parnassus Aves, San Francisco Assistant Professor of Pathology (4, 1940)
- Carter, Herbert E, M A, Ph D 452 Noyes Laboratory, Urbana, Ill Professor of Biochemistry, University of Illinois (2, 1937, 5, 1941)
- Cartland, George F, M S, Ph D The Upjohn Co, Research Dept, Kalamazoo, Mich Head, Antibiotics Research (2, 1936)
- Cary, Charles A, S B Dairy Research Laboratory, Beltsville, Md Chief, Division of Nutrition and Physiology, Bureau of Dairy Industry, U S Department of Agriculture (2, 1920)
- Cases, Albert Eugene, M D 1907 Wellington Rd, Birmingham 9, Ala Pathologist, Baptist Hospital (4, 1933)
- Cash, James Robert, M D University Hospital, Charlottesville, Va Professor of Pathology, University of Virginia (4, 1924)
- Castle, Edward S, M A, Ph D Biological Laboratories, Harvard University, Divinity Ave, Cambridge, Mass Associate Professor of General Physiology (1, 1934)

- Castle, William B, M D, S M (Hon Yale), M D (Hon Utrecht) Boston City Hospital, Boston, Mass *Professor of Medicine, Harvard Medical School, Associate Director, Thorndike Memorial Laboratory and Director, II and IV Medical Services (Harvard), Boston City Hospital* (4, 1942)
- Catchpole, Hubert Ralph, Ph D 1853 W Polk St, Chicago 12, Ill *Research Associate in Pathology, University of Chicago College of Medicine* (1, 1941)
- Cathcart, E P, M D, D Sc, LL D University of Glasgow, Glasgow, Scotland *Dean of University* (5, 1935)
- Catron, Lloyd, M D The City Hospital, Akron, O *Pathologist* (4, 1939)
- Cattell, McKeen, A M, Ph D, M D Cornell University Medical College, 1300 York Ave, New York City *Professor of Pharmacology* (1, 1923, 3, 1924)
- Cavelti, Philip A, M D Hooper Foundation, University of California Medical Center, San Francisco, Calif (6, 1947)
- Cerecedo, Leopold R, Ph D Fordham University, New York City *Professor of Biochemistry* (2, 1931, 5, 1945)
- Chadwick, Leigh Edward, Ph D Medical Division, Army Chemical Center, Md (1, 1944)
- Chaikoff, I L, A M, Ph D, M D University of California, Berkeley *Associate Professor of Physiology* (1, 1932)
- Chalkley, Harold W, A M, Ph D U S Public Health Service, National Institute of Health, Bethesda, Md *Senior Physiologist* (1, 1932)
- Chambers, Alfred H, Ph D University of Pennsylvania *Assistant Professor of Physiology*, (1, 1946)
- Chambers, Leslie Addison, M S, Ph D Camp Detrick, Frederick, Md (1, 1940)
- Chambers, Robert, A M, Ph D Marine Biological Laboratory, Woods Hole, Mass *Director of Laboratory of Cellular Physiology, Research Professor Emeritus, New York University* (1, 1932)
- Chambers, William H, M S, Ph D Medical Division, Army Chemical Center, Md *Chief, Toxicology Branch* (1, 1921, 5, 1933)
- Chandler, Caroline A, M D 615 N Wolfe St, Baltimore 5, Md *Assistant Professor of Preventive Medicine* (6, 1938)
- Chandler, Joseph P, M S, Ph D Cornell University Medical College, 1300 York Ave, New York City *Assistant Professor of Biochemistry* (2, 1944, 5, 1944)
- Chang, Min Cheuh, B Sc, Ph D Worcester Foundation, Shrewsbury, Mass *Associate Fellow* (1, 1946)
- Chanutin, Alfred, Ph D Box 1038 (University Station), Charlottesville, Va *Professor of Biochemistry, University of Virginia* (2, 1925)
- Chapman, C W, M Sc, Ph D University of Maryland, Baltimore *Professor of Pharmacology* (3, 1932)
- Chargaff, Erwin, Ph D Columbia University, College of Physicians and Surgeons, 630 W 168th St, New York City *Associate Professor of Biological Chemistry* (2, 1935)
- Charipper, Harry Adolph, M S, Ph D Washington Square College of Arts and Sciences, 100 Washington Square East, New York City *Professor of Biology and Chairman of the Department* (1, 1941)
- Chase, Aurin M, A M, Ph D Department of Biology, Princeton University, Princeton, N J *Research Associate, Assistant Professor* (1, 1939)
- Chase, Harold F, B S, M D Western Reserve University School of Medicine, Cleveland, O *Assistant Professor of Pharmacology* (3, 1944)
- Chase, Merrill W, M S, Ph D Rockefeller Institute, 66th St and York Ave, New York City *Member of Staff* (6, 1938)
- Chasis, Herbert, M D, Med Sc D 44 E 67th St, New York City *Assistant Professor of Medicine, New York University, College of Medicine* (1, 1941)
- Chatfield, Charlotte, B S Production and Marketing Admin, Food Distribution Programs Branch, U S Dept of Agriculture, Washington 25, D C *Nutritionist* (5, 1941)
- Cheldelin, Vernon H, M S, Ph D Department of Chemistry, Oregon State College, Corvallis, Ore *Associate Professor of Chemistry* (2, 1947, 5, 1946)
- Chen, Graham, Sc D, M D Puke, Davis Co, Detroit, Mich (3, 1941)
- Chen, K K, Ph D, M D The Lilly Research Laboratories, Indianapolis, Ind *Director of Pharmacological Research, Lilly Research Laboratory, Professor of Pharmacology, Indiana University School of Medicine, Indianapolis* (1, 1929, 3, 1942)
- Cheney, Ralph H M A, M S, Sc D Biology Dept, Brooklyn College, Bedford Ave and Ave H, Brooklyn 10, N Y (3, 1931)
- Chenoweth, Maynard Burton, M D Dept of Pharmacology, Cornell Univ Med College, 1300 York Ave, New York 21, N Y *Assistant Professor of Pharmacology* (3, 1945)
- Chesney, Alan M, M D The Johns Hopkins Hospital, Baltimore, Md *Dean, Johns Hopkins Medical School, Associate Professor of Medicine* (4, 1925)
- Child, Charles Manning, Ph D, D Sc (hon) Jordan Hall, Stanford University, Calif *Member, National Academy of Sciences, Professor Emeritus, University of Chicago* (1, 1923)

- Chow, Bacon F, Ph D Squibb Institute for Medical Research, New Brunswick, N J *Head of Division of Protein Chemistry* (2, 1910, 6, 1941)
- Christensen, Halvor N, M S, Ph D Children's Hospital, 300 Longwood Avenue, Boston, Mass *Director, Department of Research in Chemistry, Children's Hospital, Assistant Professor in Biological Chemistry, Harvard Medical School* (2, 1917)
- Christensen, L Royd, Ph D New York University College of Medicine, 477 First Ave, New York City *Instructor in Bacteriology* (6, 1912)
- Christian, Henry A, M D 20 Chapel St, Brookline, Mass *Hershey Professor of the Theory and Practice of Physics, Emeritus, Harvard University, Physician in Chief, Emeritus, Peter Bent Brigham Hospital, Boston, Visiting Physician, Beth Israel Hospital, Boston* (1, 1924)
- Christman, Adam A, Ph D University of Michigan Medical School, Ann Arbor *Professor of Biological Chemistry* (2, 1929)
- Chu, Wei-chang, M D 50 Hunsdale Place, New York, N J (3, 1915)
- Clark, Ada R, M A, Ph D College of Physicians and Surgeons, 630 W 168th St, New York City *Associate, Bacteriology, Teaching and Research* (6, 1936)
- Clark, Byron B, M S, Ph D Tufts College Medical School, 416 Huntington Ave, Boston 15 Mass *Professor of Pharmacology* (3, 1940)
- Clark, Elmer R, M D University of Pennsylvania, Philadelphia *Professor and Head of Department of Anatomy* (1, 1919)
- Clark, Ernest D, A M, Ph D 826 Skinner Bldg, Seattle 1, Wash *Director of the Laboratories, Northwest Branch, National Cannery Association* (2, 1912)
- Clark, George, Ph D Department of Anatomy, Chicago Medical School, 710 S Wolcott Ave, Chicago 12 Ill *Associate Professor of Neuroanatomy* (1, 1943)
- Clark, Guy W, A M, Ph D c/o Lederle Laboratories, Inc, Pearl River, N Y *Technical Director* (2, 1922)
- Clark, Janet Howell, A M, Ph D Anderson Hall, University of Rochester, Rochester, N Y *Dean of the College for Women and Professor in the Division of Biological Sciences* (1, 1922)
- Clark, Paul F, Ph D University of Wisconsin Medical School, Madison *Professor of Bacteriology* (4, 1923, 6, 1928)
- Clark, William G, Ph D Scripps Metabolic Clinic La Jolla, Calif (1, 1942)
- Clark, William Mansfield, M A, Ph D, D Sc Johns Hopkins University, Baltimore, Md *Professor of Physiological Chemistry, Member, National Academy of Sciences* (2, 1920)
- Clarke, Hans Thacher, D Sc (London), F I C 630 W 168th St, New York City *Professor of Biological Chemistry, Columbia University, College of Physicians and Surgeons* (2, 1929)
- Clarke, Robert W 6 Audubon Court, Elizabethtown, Kentucky *Physiologist, Armed Medical Research Lab, Fort Knox* (1, 1936)
- Clausen, Samuel Wolcott, M D School of Medicine, University of Rochester Rochester, N Y *Professor of Pediatrics* (2, 1922)
- Cleghorn, Robert Allen, M D, D Sc (Aberdeen) Department of Psychiatry, McGill University, Montreal, Quebec, Canada (1, 1937)
- Clowes, George Henry Alexander, Ph D, D Sc (hon), LL D (hon) Eli Lilly & Co, Indianapolis, Ind *Director of Research* (2, 1914, 6, 1919)
- Coca, Arthur F, A M, M D Pearl River, N Y *Medical Director, Lederle Laboratories* (6, 1916)
- Code, Charles F, Ph D, M D Mayo Foundation, Rochester, Minn *Professor of Physiology* (1, 1939)
- Coffey, Julia M, A B Division of Laboratories & Research, New York State Department of Health, Albany, N Y *Associate Bacteriologist* (6, 1937)
- Coghill, Robert D, M S, Ph D Abbott Laboratories North Chicago, Illinois *Director of Research* (2, 1932)
- Cohen, Barnett, M S, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore 5, Md *Associate Professor of Physiological Chemistry* (2, 1935)
- Cohen, Milton B, M D 10616 Euclid Ave, Cleveland, O *Director, The Asthma, Hay Fever and Allergy Foundation* (6, 1931)
- Cohen, Philip P, Ph D, M D Service Memorial Institute, University of Wisconsin, Madison *Associate Professor of Physiological Chemistry* (2, 1941)
- Cohen, Seymour S, Ph D Children's Hospital, 1840 Bainbridge St, Philadelphia, Pa *Assistant Professor of Physiological Chemistry, University of Pennsylvania School of Medicine* (2, 1946)
- Cohen, Sophia M, B S Division of Laboratories and Research, New York State Department of Health, Albany, N Y *Senior Bacteriologist* (6, 1935)
- Cohn, Alfred E, M D 300 Central Park W, New York City *Member, Rockefeller Institute for Medical Research* (1, 1911, 3, 1913)
- Cohn, Edwin J, Ph D, A M (Hon), Sc D (Hon) 183 Brattle St, Cambridge, Mass *Professor of Biological Chemistry, Harvard Medical School, Boston, Member, National Academy of Sciences* (1, 1919, 2, 1919)
- Cohn, Waldo E, Ph D P O Box W, Oak Ridge,

- Tenn *Principal Biochemist, Clinton Laboratories* (2, 1944)
- Cole, Harold H, M S, Ph D Division of Animal Husbandry, College of Agriculture, University of California, Davis *Professor* (1, 1947)
- Cole, Harold N, Ph B, M D 1352 Hanna Bldg, Cleveland, O *Clinical Professor of Dermatology and Syphilology, Western Reserve University* (3, 1925)
- Cole, Kenneth S, Ph D Institute of Radiobiology and Biophysics, University of Chicago, Chicago 37, Ill *Professor of Biophysics* (1, 1934)
- Cole, Versa V, Ph D, M D Indiana University School of Medicine, 1040-1232 West Michigan St, Indianapolis *Assistant Professor of Pharmacology* (3, 1941)
- Collett, Mary Elizabeth, A M, Ph D Mather College, Western Reserve University, Cleveland, O *Associate Professor of Biology* (1, 1921)
- Collier, H Bruce, M A, Ph D Dept of Biochemistry, Univ of Saskatchewan, Saskatoon, Sask *Professor of Biochemistry* (2, 1944)
- Collings, William Doyne, Ph D Medical Laboratories, State University of Iowa, Iowa City (1, 1944)
- Collins, Dean A, M A, Ph D, M D Temple Univ School of Medicine, 3400 N Broad St, Philadelphia 40, Pa *Associate Professor of Physiology* (1, 1938)
- Collins, Russell J, A M, M D, F R C P (Can) M R C P (Edin) F A C P St John, New Brunswick, Canada *Medical Superintendent of St John Tuberculosis Hospital* (3, 1915)
- Collip, J B, A M, Ph D, D Sc, M D, C B E F R S C University of Western Ontario, London, Ontario, Canada *Dean, Medical Research* (1, 1920, 2, 1920)
- Colowick Sidney P, Ph D The Public Health Research Inst of the City of New York, Inc, Foot of East 15th St, New York, N Y *Associate in the Division of Nutrition and Physiology* (2, 1944)
- Coman, Dale R, M D McManes Laboratory of Pathology, University of Pennsylvania School of Medicine, Philadelphia *Assistant Professor of Pathology* (4, 1939)
- Comroe, Julius H, Jr, M D University of Pennsylvania Graduate School of Medicine, Philadelphia *Professor of Physiology and Pharmacology* (1, 1943, 3, 1939)
- Conant, James B, Ph D 5 University Hall, Cambridge, Mass *President, Harvard University, Member, National Academy of Sciences* (2, 1932)
- Concepcion, Isabelo, M D 589 Zamora, Pasay, Rizal, Philippines *Faculty of Medicine, University Santo Tomas, Manila, Philippines*
- Professor of Biochemistry and Nutrition* (1, 1919)
- Conklin, Ruth E, M S, Ph D Vassar College Poughkeepsie, N Y *Professor of Physiology* (1, 1940)
- Conn, Jerome W, M D University of Michigan Medical School, Ann Arbor, Mich *Associate Professor of Internal Medicine* (5, 1942)
- Conrad, Ralph M, Ph D University of Denver, Denver 10, Colo (2, 1946)
- Cook, Donald Hunter, Ph D University of Miami, Coral Gables 34, Fla *Professor of Chemistry* (2, 1929)
- Cooke, Robert A, A M, Sc D (hon), M D 60 E 58th St, New York City *Director, Department of Allergy, Roosevelt Hospital* (6, 1920)
- Coolidge, Thomas B, M D, Ph D Abbot Hall, University of Chicago, Chicago 37, Ill *Associate Professor, Dept of Biochemistry, and Walter G Zoller Memorial Dental Clinic* (2, 1942)
- Coon, Julius M, Ph D Dept of Pharmacology, Univ of Chicago, Chicago 37, Ill *Instructor in Pharmacology* (3, 1911)
- Coons, Callie Mae, Ph D Bureau of Human Nutrition and Home Economics, U S Dept of Agriculture, Washington, D C *Assistant Chief* (5, 1933)
- Cope, Otis M, M D New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave at 106th St, New York City *Professor of Physiology and Biochemistry* (1, 1929)
- Copley, Alfred Lewin, M D Laboratory of Cellular Physiology, Dept of Biology, New York Univ, Washington Square, New York 3, N Y *Research Associate* (1, 1944)
- Corbin, Kendall B, M D 919 80th St, S W, Rochester, Minn *Consultant in Neurology, Mayo Clinic, Professor of Neuroanatomy, Mayo Foundation* (1, 1941)
- Corcoran, Arthur Curtis, C M, M D Cleveland Clinic Foundation, Cleveland 6, O (1, 1940)
- Corey, Edward Lyman, Ph D School of Medicine, University of Virginia, University *Assistant Professor of Physiology* (1, 1931)
- Cori, Carl F, M D Washington University School of Medicine, Kingshighway and Euclid Ave, St Louis, Mo *Professor of Biochemistry, Member, National Academy of Sciences* (2, 1925, 3, 1934)
- Cori, Gerty T, M D Washington University School of Medicine, St Louis, Mo *Professor of Biochemistry* (2, 1927, 3, 1934)
- Corley, Ralph Conner, Ph D Department of Chemistry, Purdue University, Lafayette, Ind *Professor of Biochemistry* (2, 1927)
- Corper, Harry J, M D, Ph D 1295 Clermont St, Denver, Colo *Director of Research, National Jewish Hospital* (2, 1912)

- Corson, Samuel A, M S, Ph D Department of Physiology, Howard University School of Medicine, Washington, D C (1, 1943)
- Cotts, Gerhard K, M D Lynchburg State Colony, Colony, Virginia *Clinical Director* (3, 1937)
- Co Tui, Frank, M D New York University College of Medicine, 477 First Ave, New York City *Associate Professor of Experimental Surgery* (3, 1931)
- Cournand, André Frederic, M D Civil Service, Bellevue Hospital, CD Building, 1st Ave at 28th St, New York City *Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University* (1, 1944)
- Cowgill, George Raymond, Ph D 333 Cedar St, New Haven, Conn *Professor of Nutrition, Yale University* (1, 1923, 2, 1922, 5, 1933)
- Cox, Gerald J, M S, Ph D 200 S 7th Ave, LaGrange, Ill *Research Group Leader, Corn Products Refining Co* (2, 1930, 5, 1935)
- Cox, Warren M, Jr, Ph D Mead Johnson & Co, Evansville, Ind *Director of Nutritional Research* (2, 1935, 5, 1945)
- Craig, Francis Northrop, M A, Ph D Medical Division, Army Chemical Center, Md *Physiologist* (1, 1946)
- Craig, L C, M S, Ph D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Associate Member* (2, 1935)
- Crampton, E W, Ph D Macdonald College, McGill University, Quebec, Canada *Professor of Nutrition* (5, 1940)
- Crandall, Lathan A, Jr, M D, Ph D Miles Laboratories, Inc, Elkhart, Indiana (1, 1930, 5, 1940)
- Cranston, Elizabeth M, B A, M S, Ph D Dept of Pharmacology, Univ of Minnesota Medical School, Minneapolis 14, Minn *Instructor, Dept of Pharmacology* (3, 1946)
- Cravens, W W, M S, Ph D Poultry Department, University of Wisconsin, Madison *Associate Professor of Poultry Husbandry* (5, 1947)
- Craver, Bradford N, M A, Ph D, M D Ciba Pharmaceutical Products, Inc, Lafayette Park, Summit, New Jersey *Senior Pharmacologist* (3, 1946)
- Crescitelli, Frederick, Ph B, Sc M, Ph D Dept of Zoology, Univ of Calif, Los Angeles, Calif *Physiologist* (1, 1946)
- Cressy, Norman L, M D Yale Univ School of Medicine, New Haven, Conn *Fellow in Medicine* (6, 1943)
- Cretcher, Leonard H, Ph D Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa *Assistant Director and Head of the Department of Research in Pure Chemistry* (2, 1930)
- Crider, Joseph O, M D Jefferson Medical College, Philadelphia, Pa *Associate Professor of Physiology and Assistant Dean* (1, 1935)
- Crisler, George R, Ph D, M D 157 E New England Ave, Winter Park, Fla (1, 1930)
- Crismon, Jefferson Martineau, M D Stanford University, Calif *Assistant Professor of Physiology* (1, 1944)
- Crittenden, Phoebe J, M S, Ph D Department of Physiology and Hygiene, Goucher College, Towson 4, Md (1, 1937, 3, 1937)
- Crozier, William J, Ph D Biological Laboratories, Harvard University, Cambridge, Mass *Professor of General Physiology* (1, 1923)
- Csonka, F A, Ph D Bureau of Human Nutrition and Home Economics, U S Department of Agriculture, Beltsville, Md *Senior Chemist* (2, 1924)
- Cullen, Stuart C, M D University Hospitals, Iowa City, Iowa *Assistant Professor of Surgery-Anesthesia* (3, 1944)
- Culler, Elmer A K, Ph D University of Rochester, Rochester, N Y *Professor of Psychology and Director of the Laboratory* (1, 1936)
- Cunningham, Raymond W, M S, Ph D Lederle Laboratories, Inc, Pearl River, N Y *Head, Pharmacology Research* (3, 1941)
- Cunningham, Robert Sydney, A M, M D, Sc D Albany Medical College, Albany, N Y *Professor of Anatomy and Dean* (1, 1923)
- Cureton, Thomas Kirk Jr, M A, Ph D, B P E, M P E Univ of Illinois, School of Physical Education, Urbana, Ill *Associate Professor of Physical Education* (1, 1946)
- Curnen, Edward C, M D Yale Univ School of Medicine, New Haven 11, Conn (6, 1941)
- Curtis, George Morris, M A, Ph D, M D Kinsman Hall, Ohio State University, Columbus *Professor of Surgery, Chairman, Department of Research Surgery* (1, 1933, 4, 1933)
- Curtis, Howard J, M A, Ph D Vanderbilt University School of Medicine, Nashville 4, Tenn *Professor of Physiology* (1, 1940)
- Cutting, Reginald A, M D, Ph D Georgetown University School of Medicine, 3900 Reservoir Road, N W, Washington, D C *Professor of Physiology and Director of the Department* (1, 1939)
- Cutting, Windsor C, M D Stanford University School of Medicine, San Francisco, Calif *Assistant Professor of Therapeutics* (3, 1939)
- Daft, Floyd Shelton, Ph D National Institute of Health, Washington, D C *Senior Scientist* (5, 1941)
- Daggs, Ray Gilbert, Ph D Medical Dept, Field Research Lab, Fort Knox, Kentucky *Director of Research* (1, 1935, 5, 1933)



- Dakin, Henry D**, D Sc, LL D, Ph D, F I C, F R S Scarborough-on-Hudson, N Y (2, 1906)
- Dalldorf, Gilbert, M D** New York State Department of Health, Albany, N Y *Director, Division of Laboratories and Research* (4, 1947)
- Dalton, Albert J**, M A, Ph D National Institute of Health, Bethesda, Md *Cytologist* (4, 1942)
- Dam, Henrik, D Sc** Biologisk Afdeling Danmarks Tekniske Højskole, Østervoldgade 10 I, Copenhagen, K, Denmark *Professor* (2, 1944, 5, 1913)
- D'Amour, Fred E**, M S, Ph D 2311 S Josephine St, Denver, Colo *Associate Professor, Department of Zoology, University of Denver* (1, 1934)
- D'Amour, Marie C**, Ph D, M D 2311 So Josephine St, Denver, Colo (1, 1934)
- D'Angelo, Savino A**, M S, Ph D Department of Biology, New York University, Washington Square, New York 3, N Y *Assistant Professor of Biology* (1, 1947)
- Daniels, Amy L**, Ph D 720 N Van Buren St, Iowa City, Iowa *Retired* (2, 1919, 5, 1933)
- Danielson, Irvin S**, Ph D Pearl River Apartments, Apt 3H, Pearl River, N Y *Research Chemist* (2, 1937)
- Dann, W J**, Ph D, D Sc Duke University School of Medicine, Durham, N C *Professor of Nutrition* (2, 1937, 5, 1938)
- Danowski, T S**, M D University of Pittsburgh School of Medicine, Pittsburgh, Pa *Renzelhausen Professor of Research Medicine* (1, 1947)
- Darby, William J**, M D, Ph D Vanderbilt Univ School of Medicine, Nashville, Tenn *Associate Professor of Biochemistry, Assistant Professor of Medicine* (5, 1945)
- Darling, Robert Croly, M D** 157 Glenwood Ave, Leona, N J Dept of Medicine, Columbia Univ College of Physicians and Surgeons, New York, 32, N Y (1, 1944)
- Darrow, Chester W**, Ph D Institute for Juvenile Research, 907 S Wolcott St, Chicago, Ill *Research Psychologist, Institute for Juvenile Research, Associate in Physiology, University of Illinois College of Medicine* (1, 1937)
- Darrow, Daniel Cady, M D** New Haven Hospital, New Haven, Conn *Associate Professor of Pediatrics, Yale University* (2, 1936)
- Daubert, B F**, Ph D University of Pittsburgh, Pittsburgh, Penn *Research Professor* (2, 1947)
- Davenport, Horace Willard, B S, B Sc (Oxon) Ph D** Dept of Physiology, University of Utah, Salt Lake City 1 (1, 1942)
- David, Norman Austin, M D** University of Oregon Medical School, Portland *Professor of Pharmacology* (3, 1934)
- Davidsohn, Israel, M D** Mount Sinai Hospital, 2750 W 15th Place, Chicago, Ill *Pathologist and Director of Laboratories, Mt Sinai Hospital, Associate Professor of Pathology, College of Medicine, University of Illinois* (4, 1939, 6, 1929)
- Davis, George Kelso, Ph D** Nutrition Laboratory, Animal Industry Dept, Agricultural Experiment Station, Gainesville, Fla *Nutritional Technologist and Biochemist, Professor of Nutrition, Univ of Florida, Florida Agricultural Experiment Station* (5, 1944)
- Davis, Hallowell, M D** Central Institute for the Deaf, 818 S Kingshighway, St Louis 10, Mo (1, 1925)
- Davis, Harry A**, M D, C M Dept of Surgery, College of Medical Evangelists, Boyle and Michigan Avenues, Los Angeles 33, Calif (4, 1944)
- Davis, John Emerson, M S, Ph D** Univ of Arkansas School of Medicine, Little Rock *Professor of Pharmacology and Physiology* (1, 1941, 3, 1941)
- Dawson, Charles R**, Ph D 411 Havemeyer Hall, Columbia University, New York 27, N Y *Associate Professor of Organic Chemistry* (2, 1946)
- Dawson, James Robertson, Jr, M D** Vanderbilt Medical School, Nashville, Tenn *Professor of Pathology* (4, 1910)
- Dawson, Percy M**, M D 665 L Maryland Ave, Claremont, Calif (1, 1900)
- Day, Harry G**, D Sc Indiana University, Bloomington *Associate Professor, Dept of Chemistry* (5, 1910)
- Day, Paul L**, M A, Ph D University of Arkansas School of Medicine, Little Rock *Professor of Physiological Chemistry* (2, 1934, 5, 1933)
- Dearborn, Earl H**, M A, Ph D Johns Hopkins Univ School of Medicine, 710 N Washington St, Baltimore 5, Md *Instructor in Pharmacology and Experimental Therapeutics* (3, 1946)
- de Beer, Edwin J**, Ph D The Wellcome Research Laboratories, Tuckahoe, N Y *Assistant Director of Research* (3, 1944)
- De Bodo, Richard C**, M D 477 First Ave, New York, N Y *Associate Professor of Pharmacology, New York Univ College of Medicine* (1, 1932, 3, 1931)
- De Boer, Benjamin, M A, Ph D** St Louis University School of Medicine, 1402 South Grand Blvd, St Louis 4, Mo *Assistant Professor of Pharmacology* (1, 1947)
- DeEds, Floyd, M A, Ph D** 344 Santa Ana Ave, San Francisco, Calif *Principal Pharmacologist, Western Regional Research Laboratory, 800 Buchanan St, Albany, Calif* (2, 1937, 3, 1927)
- Defendorf, James Holmes, Ph D** Office of the Chief of the Chemical Warfare Service, Washington, D C *Colonel, Sn C* (3, 1940)

- de Gara, Paul F, M D 200 Pinchurst Ave, New York City *Instructor in Pathology, Cornell University Medical College, Physician, New York Hospital* (6, 1911)
- DeGraff, Arthur C, M D New York University College of Medicine, New York City *Professor of Therapeutics* (3, 1937)
- de Gutierrez-Mahoney, C G, M D St Vincent's Hospital, New York, N Y *Director, Neurological Division and Neurosurgeon in Chief* (1, 1940, 4, 1941)
- Deichmann, William B, M Sc, Ph D Albany Medical College, Albany, N Y *Associate Professor of Pharmacology and Head, Division of Pharmacology* (3, 1911)
- del Pozo, E C, M D Medellin 196, Mexico, D F, Mexico (1, 1943)
- Dempsey, Edward W, Sc M, Ph D Harvard Medical School, Boston, Mass *Associate Professor of Anatomy* (1, 1910)
- Derbyshire, Arthur J, Ph D EEG Department, Harper Hospital, Detroit, Mich (1, 1939)
- de Savitsch, Eugene, M D Suite 24, 1150 Connecticut Ave, Washington, D C *Clinical Instructor in Surgery, Georgetown University School of Medicine Consulting Surgeon, Home of Incurables, Surgeon, Doctors Hospital* (1, 1934)
- Dettwiler, Herman A, M S, Ph D Eli Lilly and Co, Indianapolis, Ind *Research Bacteriologist, Biological Division* (6, 1946)
- Deuel, Harry J, Jr, Ph D University of Southern California Medical School, Los Angeles *Professor of Biochemistry* (1, 1928, 2, 1924, 5, 1933)
- Deulofeu, Venancio, D Chem Casilla Correo 2539, Buenos Aires, Argentina *Professor of Organic Chemistry, University of Buenos Aires* (2, 1942)
- Dey, Frederick L, Ph D, M D Box 11, Submarine Base, New London, Conn Lt (jg), U S N R (1, 1945)
- Dickison, H L, M A, Ph D Bristol Laboratories, Inc, Syracuse, N Y (3, 1946)
- Dieckmann, William J, M D The Chicago Living-In Hospital, 5841 Maryland Avenue, Chicago 37, Ill *Mary Campbell Ryerson Professor and Chairman of the Department of Obstetrics and Gynecology, University of Chicago* (3, 1947)
- Dienes, Louis, M D Massachusetts General Hospital, Boston *Bacteriologist* (6, 1924)
- Dill, David Bruce, M A, Ph D Medical Division, Army Chemical Center, Md *Scientific Director* (1, 1941, 2, 1927, 5, 1936)
- Dille James M, M S, Ph D, M D Univ of Washington School of Medicine, Seattle 5, Wash *Professor of Pharmacology, Assistant Dean* (3, 1939)
- Dillon, Robert T, M S, Ph D % G D Searle and Co, Box 5110, Chicago 80, Ill *Head, Analytical Division* (2, 1934)
- Dingle, John H, Sc D, M D Western Reserve University School of Medicine, Cleveland 6, Ohio *Professor of Preventive Medicine* (6, 1911)
- Di Palma, Joseph R, M D Long Island College of Medicine, 350 Henry St, Brooklyn, N Y *Associate in Physiology* (1, 1943)
- Dische, Zacharias, M D Dept of Biochemistry, College of Physicians and Surgeons, 630 W 168th St, New York City (2, 1944)
- Dixon, Harold M, M D U S Naval Hospital, Philadelphia 4, Pa *Associate in Pathology, Chief of the Division of Pathology, Phila General Hospital* (4, 1936)
- Doan, Charles A, M D Ohio State University, College of Medicine, Columbus *Dean, Professor of Medicine, Director of Medical Research* (4, 1928)
- Dobriner, Konrad, M D Sloan Kettering Institute, 411 E 68th St, New York 21, N Y *Member* (2, 1946)
- Dochez, A Raymond, M D, Sc D (hon) Presbyterian Hospital, 620 W 168th St, New York City *John E Borne Professor of Medical and Surgical Research, Columbia University, Member of National Academy of Sciences* (4, 1917, 6, 1922)
- Dohan, F Curtis, M D 80 Princeton Rd, Cynwyd, Pa *Fellow, George S Cox Medical Research Institute, Associate in Medicine, University of Pennsylvania, Philadelphia* (1, 1941)
- Doisy, Edward A, M S, Ph D, Sc D St Louis University School of Medicine, St Louis 4, Mo *Professor of Biological Chemistry, Member, National Academy of Sciences* (2, 1920)
- Dolman, C E, D P H, Ph D The University of British Columbia, Vancouver, B C, Canada *Professor of Bacteriology and Preventive Medicine* (6, 1947)
- Dominguez, Rafael, M D Saint Luke's Hospital, 11311 Shaker Blvd, Cleveland, O *Director of Laboratories, St Luke's Hospital, Associate in Pathology, Western Reserve University* (1, 1935)
- Donahue, D D, D Sc Division of Industrial Hygiene, National Institute of Health, Bethesda, Md *Physiologist, Toxicology Section, Division of Industrial Hygiene, U S Public Health Service* (3, 1941)
- Donelson, Eva G, Ph D The Ohio State University, Columbus, Ohio *Professor of Home Economics* (5, 1947)
- Dooley, M S, M D 417 Waverly Ave, Syracuse 10, N Y *Professor of Pharmacology, College of Medicine, Syracuse University* (3, 1923)
- Dorfman, Ralph I, Ph D Dept of Biochemistry, Western Reserve University School of Medicine,

- Cleveland, O *Assistant Professor of Biochemistry* (2, 1940)
- Dotti, Louis Basil, M A , Ph D St Luke's Hospital, Amsterdam Ave and 113th St , New York City *Chemist, St Luke's Hospital, Lecturer in Physiology and Biochemistry, New York Medical College* (1, 1937)
- Doty, J Roy, Ph D American Dental Association, 222 E Superior St , Chicago, Ill *Senior Chemist* (2, 1941)
- Doudoroff, Michael, M A , Ph D Dept of Bacteriology, 3531 Life Science Bldg , Univ of Calif , Berkeley, Calif *Associate Professor of Bacteriology* (2, 1946)
- Dounce, Alexander L , Ph D Strong Memorial Hospital, 260 Crittenden Blvd , Rochester, N Y *Instructor in Biochemistry, University of Rochester, School of Medicine and Dentistry* (2, 1944)
- Dow, Philip, Ph D University of Georgia School of Medicine, Augusta *Associate Professor of Physiology* (1, 1939)
- Dow, Robert S , M D , Ph D University of Oregon Medical School, Portland *Associate Professor of Anatomy* (1, 1940)
- Downs, Ardrey W , M A , M D , D Sc , F A C P University of Alberta, Edmonton, Canada *Professor of Physiology and Pharmacology* (1, 1917)
- Downs, Cora M , Ph D 1625 Alabama St , Lawrence, Kan (6, 1929)
- Doyle, William Lewis, M A , Ph D 930 East 58th St , Chicago 37, Ill *Associate Professor of Anatomy, University of Chicago* (1, 1946)
- Drabkin, David L , M D Graduate School of Medicine, University of Pennsylvania, Philadelphia *Professor of Physiological Chemistry* (2, 1928, 5, 1934)
- Dragstedt, Carl A , Ph D , M D Northwestern University Medical School, 303 E Chicago Ave , Chicago, Ill *Professor of Pharmacology* (1, 1928, 3, 1932)
- Dragstedt, Lester R , M D , Ph D University of Chicago, Chicago, Ill *Professor of Surgery* (1, 1920)
- Draize, J H , Ph D Division of Pharmacology, Food & Drug Administration, U S Dept of Agriculture, Washington, D C *Pharmacologist* (3, 1940)
- Drake, T G H , M B , F R C P (c) University of Toronto, Toronto, Canada *Junior Demonstrator in Paediatrics, Department of Medicine, University of Toronto, Clinical Assistant on Active Staff and Associate Director Research Laboratory, Hospital for Sick Children* (5, 1936)
- Draper, William B , M Sc , M D University of Colorado School of Medicine, 4200 E 9th Ave , Denver *Associate Professor of Physiology and Pharmacology* (1, 1947, 3, 1938)
- Dreisbach, Robert H , Ph D , M D Stanford University School of Medicine, San Francisco 15, Calif *Instructor On leave Capt , MC, 0491982, Lovell General Hospital, Ft Devens, Mass* (3, 1945)
- Dreyer, Nicholas Bernard, M A (Oxon) School of Medicine, University of Vermont, Burlington *Associate Professor of Physiology and Pharmacology* (3, 1942)
- Drill, Victor Alexander, Ph D Dept of Pharmacology, Yale University School of Medicine, 333 Cedar St , New Haven, Conn *Instructor in Pharmacology* (1, 1943, 3, 1946)
- Drinker, Cecil K , M D Harvard University School of Public Health, Boston, Mass *Professor of Physiology and Dean* (1, 1915)
- Dripps, Robert D , M D School of Medicine, University of Pennsylvania, Philadelphia *Associate Professor of Anesthesiology, Director of Anesthesia, Hospital of the University of Pennsylvania* (1, 1947, 3, 1945)
- Driver, Robert L , M S , Ph D Department of Pharmacology and Experimental Therapeutics, University of California School of Medicine, San Francisco 22 *Lecturer in Pharmacology* (1, 1945, 3, 1947)
- Drury, Douglas R , M D University of Southern California, Los Angeles *Professor of Physiology* (1, 1932)
- Dubin, Harry E , Ph D 11 W 42nd St , New York 18, N Y *President, H E Dubin Laboratories, Inc* (2, 1925)
- Dubin, Isadore N , M D Institute of Pathology, University of Tennessee, Memphis 7, Tenn *Assistant Professor of Pathology and Bacteriology* (4, 1947)
- Dubnoff, Jacob W , M A , Ph D 1201 L California St , Pasadena 4, Calif *Senior Research Fellow, California Institute of Technology* (2, 1946)
- DuBois, Eugene F , M D Cornell University Medical School, 1300 York Ave , New York, N Y *Professor and Head of the Department of Physiology and Biophysics, Attending Physician, New York Hospital, Member, National Academy of Sciences* (1, 1913, 3, 1921, 5, 1935)
- Du Bois, Kenneth P , B S M S , Ph D Dept of Pharmacology, Univ of Chicago, Chicago 37, Ill *Instructor in Pharmacology* (3, 1946)
- Dubos, Rene J , Ph D , D Sc Rockefeller Institute for Medical Research, 66th St and York Ave , New York City *Head, Dept of Bacteriology* (6, 1938)
- Dugal, L Paul, M A , M Sc , Ph D Research Department on Acclimatization, Medical School, Laval University, Quebec City, Canada *Research Professor and Head of the Research De-*

- partment on Acclimatization, Associate Director of the Institute of Hygiene (1, 1947)
- Dukes, H H, DVM, MS New York State Veterinary College, Cornell University, Ithaca, N Y Professor of Veterinary Physiology (1, 1934)
- Dulaney, Anna D, AM, PhD Pathological Institute, University of Tennessee, Memphis Assistant Professor of Bacteriology, Medical School (6, 1924)
- Dumke, Paul Rudolph, MD Clinical Research Section, Medical Research Lab, Edgewood Arsenal, Edgewood, Md Instructor in Pharmacology, University of Pennsylvania, Captain, MC (3, 1942)
- Dunlap, Charles L, MD Tulane University of Louisiana, 1430 Tulane Ave, New Orleans Professor of Pathology and Bacteriology (1, 1942)
- Dunn, Max Shaw, PhD University of California, Los Angeles Professor of Chemistry (2, 1933)
- Dunn, Thelma Brumfield, MD The National Cancer Institute, Bethesda, Md Pathologist (4, 1945)
- Durrant, Edwin Poe, MA PhD Ohio State University, Columbus Emeritus Associate Professor of Physiology (1, 1928)
- Dutcher, James D, MS, PhD The Squibb Institute for Medical Research, New Brunswick, New Jersey Research Associate, Division of Organic Chemistry (2, 1946)
- Dutcher, R Adams, MS, MA, DSc Pennsylvania State College, State College Professor and Head of Department of Agricultural and Biological Chemistry (2, 1920, 5, 1933)
- Duval, Charles Warren, MD San José Hospital, San Jose, Calif Professor Emeritus of Pathology and Bacteriology, Tulane Univ, New Orleans, La Director, Laboratory of Pathology, San Jose Hospital (4, 1913)
- du Vigneaud, Vincent, MS, PhD Cornell University Medical College, 1300 York Ave, New York 21, N Y Professor of Biochemistry, Member, National Academy of Sciences (2, 1929, 5, 1934)
- Dworkin, Simon, DDS, MD, CM Biology Building, McGill University, Montreal, Quebec, Canada Lecturer in Physiology, Faculty of Medicine (1, 1931)
- Dye, J A, PhD James Law Hall, Cornell University, Ithaca, N Y Professor of Physiology (1, 1929)
- Dye, Marie, MS, PhD Michigan State College, East Lansing Dean, School of Home Economics (2, 1929, 5, 1933)
- Dyer, Helen M, MS, PhD National Cancer Institute, NIH USPHS, Bethesda, Md Biochemist (2, 1936, 5, 1937)
- Eadie, George S, PhD Duke University School of Medicine, Box 3709, Durham, N C Professor of Physiology and Pharmacology (1, 1929, 3, 1940)
- Eagle, Harry, AB, MD National Cancer Institute, Bethesda, Md Scientific Director (3, 1946, 4, 1936, 6, 1946)
- Earle, D P, Jr, MD, Med Sc D New York University College of Medicine, 477 First Avenue, New York 16, N Y Associate Professor of Medicine (1, 1947)
- Earle, Wilton R, PhD US Public Health Service, National Cancer Institute, Bethesda, Md Principal Cytologist (4, 1940)
- Eaton, Monroe D, MD Harvard Medical School, 25 Shattuck St, Boston 15, Mass (6, 1937)
- Ecker, E E, PhD School of Medicine, Western Reserve University, 2085 Adelbert Rd, Cleveland, O Professor of Immunology (4, 1925, 6, 1947)
- Eckstein, Henry C, MS, PhD 320 W Medical Building, University of Michigan, Ann Arbor Associate Professor of Biological Chemistry (2, 1925)
- Eckstein, R W, MA, MD Department of Medicine, Western Reserve University, Cleveland, Ohio Senior Instructor, in charge of Cardiovascular Experimental Medical Research Laboratory (1, 1947)
- Eddy, Nathan B, MD National Institute of Health, Bethesda, Md Principal Pharmacologist, United States Public Health Service (3, 1929)
- Eddy, Walter H, AM, PhD American Chlorophyll, Inc, Lake Worth, Fla Director of Research (2, 1913, 5, 1933)
- Edsall, Geoffrey, MD Antitoxin and Vaccine Laboratory, 375 South St, Jamaica Plain, Mass Acting Director, Division of Biologic Laboratories, Massachusetts Department of Public Health, Associate in Public Health Laboratory Methods, Simmons College, Instructor in Applied Immunology, Harvard School of Public Health (6, 1943)
- Edsall, John Tileston, MD Harvard Medical School, Boston, Mass Associate Professor of Biological Chemistry and Tutor in Biochemical Sciences (2, 1931)
- Edwards, Dayton J, PhD Cornell University Medical College, 1300 York Ave, New York City Associate Professor of Physiology, Assistant Dean (1, 1921)
- Edwards, Jesse E, MD Mayo Clinic, (Sert Path Anat) Rochester 4, Minn Assistant Professor of Pathologic Anatomy, Mayo Foundation, Graduate School, University of Minnesota (4, 1941)
- Edwards, J Graham, AM, PhD 24 High St,

- Fell, Norbert, Ph D Camp Detrick, Frederick, Maryland *Chief, Pilot Plant Division* (6, 1944)
- Feller, A E, M D Western Reserve School of Medicine, Cleveland 6, Ohio *Assistant Professor of Preventive Medicine* (6, 1943)
- Fellows, Edwin J, M S, Ph D Temple University School of Medicine, Philadelphia, Pa *Assistant Professor of Pharmacology* (3, 1939)
- Felton, Lloyd D, M D, D Sc National Institute of Health, Bethesda, Md *Medical Director, USPHS* (6, 1926)
- Fenn, Wallace Osgood, A M, Ph D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd, Rochester, N Y *Professor of Physiology, Member, National Academy of Sciences* (1, 1924)
- Fenning, Con, M D, M A University of Utah School of Medicine, Salt Lake City *Professor of Pharmacology and Physiology* (1, 1942)
- Fenton, P F, M S, Ph D Department of Physiological Chemistry, Yale University School of Medicine, New Haven 11, Conn *Research Assistant* (1, 1947)
- Ferguson, James Kenneth Wallace, M A, M D 76 Kilbarry Rd, Toronto, Ontario, Canada *Professor and Head of Department of Pharmacology, University of Toronto* (1, 1933, 3, 1941)
- Ferguson, John Howard, M D, M A, L M S S A Dept of Physiology, School of Medicine, University of North Carolina, Chapel Hill *Professor of Physiology and Acting Professor of Pharmacology* (1, 1933)
- Ferguson, L Kraeer, M D 133 S 36th St, Philadelphia 4, Pa *Professor of Surgery, Graduate School, Univ of Pennsylvania, and Woman's Medical College of Pennsylvania, Surgeon, Doctors Hospital and Woman's Medical College, Graduate Hosp, Philadelphia General Hospital* (4, 1935)
- Ferry, John Douglass, Ph D, Dept of Chemistry, Univ of Wisconsin, Madison 6, Wis *Associate Professor of Chemistry* (2, 1941)
- Ferry, Ronald M, M D 966 Memorial Drive Cambridge, Mass *Associate Professor of Biochemistry* (2, 1924)
- Fetcher, Edwin S, Ph D R D #4, Xenia, Ohio (1, 1944)
- Fetter, Dorothy, Ph D Department of Hygiene, Brooklyn College, Brooklyn, N Y *Instructor in Physiology* (1, 1944)
- Fevold, Harry L, M S, Ph D 1849 W Pershing Road, Chicago 9, Ill *Chief, Food Research Division, Quartermaster Food and Containers Institute* (2, 1942)
- Field, John, II, A M, Ph D Department of Physiology, Stanford University, Stanford, Calif *Professor of Physiology* (1, 1930)
- Fincke, Margaret L, Ph D Oregon State College, Corvallis *Associate Professor of Foods and Nutrition, School of Home Economics* (5, 1940)
- Findley, Thomas, Jr, M D Ochsner Clinic, 3503 Prytania, New Orleans, La *Head of the Department of Internal Medicine, Ochsner Clinic, New Orleans, Assistant Professor of Clinical Medicine, Tulane University School of Medicine* (1, 1938)
- Finerty, John C, M S, Ph D Department of Anatomy, Washington University School of Medicine, St Louis 10, Mo *Assistant Professor of Anatomy* (1, 1947)
- Finland, Maxwell, B S Boston City Hospital, Boston, Mass *Assistant Professor of Medicine, Harvard Medical School* (6, 1941)
- Finnegan, J K, M S, Ph D Medical College of Virginia, Richmond 19, Va *Assistant Professor of Pharmacology* (3, 1947)
- Firor, Warfield Monroe, M D Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Surgery, Johns Hopkins University* (1, 1932)
- Fischer, Ernst, M D, Dr habil Medical College of Virginia, Richmond *Professor of Physiology* (1, 1936)
- Fischer, Hermann O L, Ph D Banting Institute, 100 College St, University of Toronto, Toronto 5, Canada *Research Professor of Organic Chemistry* (2, 1940)
- Fischer, Martin H, M D, Pharm D (hon), Sc D University of Cincinnati College of Medicine, Eden Ave, Cincinnati 19, O *Professor of Physiology* (1, 1901, 2, 1919)
- Fishberg, Ella H, M A, M D Beth Israel Hospital, Stuyvesant Park East, New York City *Biochemist* (2, 1931)
- Fisher, Albert Madden, M A, Ph D Connaught Laboratories, University of Toronto, Toronto, Canada *Research Associate* (2, 1944)
- Fisher, Kenneth C, M A, Ph D University of Toronto, Toronto, Ont, Canada *Assistant Professor of Physiological Zoology* (1, 1940)
- Fishman, William H, Ph D University of Chicago Medical School, Chicago, Ill *Research Associate and Assistant Professor in Biochemistry* (2, 1947)
- Fiske, Cyrus H, M D Harvard Medical School, Boston, Mass *Professor of Biological Chemistry* (2, 1914)
- Fitzhugh, O Garth, Ph D Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D C *Pharmacologist* (3, 1940)
- Fleischmann, Walter, M D, Ph D Medical Division, Army Chemical Center, Md *Chief, Physiology Section, Instructor in Pediatrics, Johns Hopkins University* (1, 1940)
- Fleisher, Moyer S, M D Jewish Hospital, St

- Louis, Mo *Research Bacteriologist* (4, 1924, 6, 1932)
- Flexner, Louis B, M D Department of Embryology, Carnegie Institution of Washington, Wolfe and Madison Sts, Baltimore, Md *Research Associate* (1, 1933)
- Floek, Eunice V, Ph D Mayo Clinic, Rochester, Minn *Associate Professor in Experimental Medicine, Mayo Foundation, Univ of Minnesota* (2, 1940)
- Florman, Alfred L, M D Hospital of the Rockefeller Institute, New York, N Y *Visiting Investigator* (6, 1942)
- Flosdorf, Earl W, Ph D Forest Grove, Bucks Co, Pa *Research—University of Pennsylvania School of Medicine* (6, 1941)
- Floyd, Cleveland, M D, Sc D 246 Marlborough St, Boston, Mass *Chief Examiner, Boston Health Dept* (6, 1916)
- Foa, Piero Pio, Ph D 710 S Wolcott St, Chicago Ill *Associate Professor of Physiology and Pharmacology, Chicago Medical School* (1, 1944)
- Folch, Jordi, M D McLean Hospital, Waverly, Mass *Assistant Professor of Biological Chemistry, Harvard Medical School Director of Scientific Research, McLean Hospital* (2, 1941)
- Folkers, Karl, Ph D Merck and Co, Inc Rahway, N J *Director of Organic and Biochemical Research* (2, 1947)
- Follensby, Edna M, Ph G 80 E Concord St, Boston, Mass *Research Assistant, Evans Memorial Special Instructor in Biology, Simmons College* (6, 1933)
- Follis, Richard H, Jr, M D School of Medicine, Johns Hopkins University *Associate Professor of Pathology* (4, 1942)
- Fontane, Thomas Davis, Ph D Biologically Active Compounds Division, Room 114 North Bldg, Agricultural Research Center, Beltsville, Md *Chemist, Bureau of Agricultural and Industrial Chemistry, U S Dept of Agriculture* (2, 1946)
- Foot, Nathan Chandler, M D 1300 York Ave, New York 21, N Y *Professor of Surgical Pathology, Cornell University Medical College, Surgical Pathologist, New York Hospital* (4, 1924)
- Forbes, Alexander, A M, M D Harvard Medical School, Boston, Mass *Professor of Physiology, Member of the National Academy of Sciences* (1, 1910)
- Forbes, Ernest B, Ph D State College, Pa *Professor Emeritus Animal Nutrition* (1, 1917, 5, 1935)
- Forbes, Henry S, M D Forest St, Milton 86, Mass *Associate in Neuropathology, Harvard Medical School, Boston* (1, 1931)
- Forbes, John C, M A, Ph D Medical College of Virginia, Richmond *Research Professor of Biochemistry* (2, 1937)
- Forbes, William H, M A, Ph D Harvard University, Fatigue Laboratory, Boston, Mass *Research Fellow, Assistant Director of Fatigue Lab, Assistant Professor of Industrial Physiology* (1, 1943)
- Fosdick, Leonard S, Ph D 311 E Chicago Ave, Chicago, Ill *Professor of Chemistry, Northwestern University* (2, 1944)
- Foster, G L, Ph D College of Physicians and Surgeons, 630 W 168th St, New York City *Professor of Biological Chemistry* (2, 1923)
- Foster, Harry E, M D Cutter Laboratory, Berkeley, Calif *Medical Director* (6, 1913)
- Foster, Jackson W Dept of Botany and Bacteriology, Univ of Texas, Austin 12, Texas *Associate Professor of Bacteriology* (2, 1946)
- Foster, Robert H K, Ph D, M D St Louis University School of Medicine, St Louis, Mo *Associate Professor of Pharmacology* (1, 1940, 3, 1944)
- Foster, Ruth A C, Ph D Dept of Botany and Bacteriology, University of Texas, Austin *Instructor* (6, 1943)
- Fothergill, LeRoy D, M D Camp Detrick, Frederick, Maryland (6, 1936)
- Fox, Sidney W, Ph D Chemistry Dept, Iowa State College, Ames, Iowa *Professor of Chemistry and Research Professor, Chemistry Section, Iowa Agricultural Experiment Station, Research Professor of Chemistry, Industrial Science Research Institute, Iowa State College* (2, 1946)
- Fraenkel-Conrat, Heinz, M D, Ph D Western Regional Research Laboratory U S Dept of Agriculture, Albany 6, Calif *Chemist* (2, 1942)
- Francis, Thomas, Jr, M D, M S (hon), Sc D (hon) School of Public Health, University of Michigan, Ann Arbor *Professor of Epidemiology* (4, 1940, 6, 1930)
- Franke, Florent E, M D 9 Sylvester, Webster Groves, Mo *Assistant Professor of Physiology, St Louis University School of Medicine* (1, 1934)
- Frankel, Edward M, Ph D 214 River Rd, Nyack, N Y *Consulting Chemist* (2, 1916)
- Fraps, R M, Ph D Bureau of Animal Husbandry, Beltsville, Md *Senior Physiologist* (1, 1947)
- Fraser, Alexander MacLeod, A M, M D, C M McGill University, Montreal, Canada *Lecturer in Pharmacology* (3, 1939)
- Fraser, Donald T, M B Connaught Laboratories, University of Toronto, Toronto 5, Canada *Professor of Hygiene and Preventive Medicine* (6, 1935)
- Frear, Donald E, M S, Ph D Dept of Agricultural and Biological Chemistry The Pennsyl

- vania State College, State College, Pa *Professor of Agriculture and Biological Chemistry* (2, 1946)
- Free, Alfred H, M S, Ph D Research Laboratory, Miles Laboratories, Inc, Elkhart, Ind *Head of Biochemistry Section* (2, 1946, 5, 1941)
- Freeman, Harry, M D Worcester State Hospital, Worcester, Mass *Internist, Research Service* (1, 1939)
- Freeman, Leslie Willard, Ph D, M D 789 Howard Ave, Department of Surgery, Yale University School of Medicine, New Haven 11, Conn (1, 1944)
- Freeman, Norman E, M D Department of Surgery, University of California Medical School, San Francisco 22 (1, 1936)
- Freeman, Smith, M D, Ph D Northwestern University School of Medicine, 303 E Chicago Ave, Chicago, Ill *Assistant Professor of Physiology and Pharmacology* (1, 1937)
- French, C S, Ph D Carnegie Institution of Washington, Stanford University, Calif *Director, Division of Plant Biology* (1, 1947, 2, 1946)
- Freund, Jules, M D Public Health Research Institute of the City of New York, Foot of E 15th St, New York, N Y *Member* (4, 1930, 6, 1924)
- Friedemann, Theodore E, M A, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Associate Professor of Physiology* (2, 1925)
- Friedemann, Ulrich, M D Department of Bacteriology, The Jewish Hospital of Brooklyn, Classon and St Marks Ave, Brooklyn, N Y (6, 1938)
- Friedenwald, Jonas S, M D, M A 1212 Lutw Place, Baltimore 17, Md The Johns Hopkins Hospital, Baltimore *Associate Professor of Ophthalmology* (1, 1947)
- Friedewald, William F, M D Emory University School of Medicine, Atlanta, Ga *Professor of Bacteriology, Associate Professor of Medicine* (4, 1941)
- Friedgood, Harry B, M D 2943 Queensburg Road, Los Angeles 34, Calif *Assistant Clinical Professor of Medicine, Univ of Southern Calif Med School, Senior Attending Physician, Los Angeles County Hospital* (1, 1936)
- Friedman, Maurice H, Ph D, M D 2040 Belmont Rd, Washington 9, D C (1, 1929)
- Friedman, Meyer, M D Harold Brunn Institute for Cardiovascular Research, Mt Zion Hospital, 2200 Post St, San Francisco, Calif *Director* (1, 1947)
- Friedman, M H F, M A, Ph D Jefferson Medical College of Philadelphia, 1025 Walnut St, Philadelphia, Pa *Assistant Professor of Physiology* (1, 1941)
- Friedman, Nathan B, M D Cedars of Lebanon Hospital, Los Angeles, Calif (4, 1942)
- Friedman, Sydney M, M D, Ph D Department of Anatomy, McGill University, Montreal 2, Canada *Assistant Professor of Anatomy* (1, 1917)
- Frost, Douglas Van Anden, M A, Ph D Abbott Laboratories, North Chicago, Ill *Head of Nutritional Research* (2, 1946, 5, 1947)
- Fruton, J S, Ph D Yale School of Medicine, 333 Cedar St, New Haven, Conn *Associate Professor of Physiological Chemistry* (2, 1938)
- Fugo, Nicholas W, M S, Ph D Department of Obstetrics and Gynecology, University of Chicago, Chicago, Ill (3, 1944)
- Fuhrman, Frederick A, M S, Ph D Dept, of Physiology, Stanford Univ, Stanford University, Calif *Instructor in Physiology* (1, 1946)
- Fulton, John Farquhar, M A, Ph D, M D Yale University School of Medicine, New Haven, Conn *Sterling Professor of Physiology* (1, 1925)
- Funk, Casimir, D Sc, Ph D 186 Riverside Drive, New York 24, N Y (2, 1921)
- Furth, Jacob, M D Cornell University Medical College, 1300 York Ave, New York, N Y *Professor of Pathology* (1, 1932, 6, 1930)
- Gaebler, Oliver H, Ph D, M D Henry Ford Hospital, Detroit, Mich *Head, Department of Biochemistry, Research Institute* (2, 1927)
- Gaffron, Hans, Ph D Department of Chemistry, University of Chicago, Chicago, Ill *Associate Professor of Biochemistry* (2, 1941)
- Gagge, Adolf Pharo, Ph D Aeromedical Research Laboratory, Wright Field, Dayton, O *Lt Col, Chief, Biophysics Branch, Air Corps, U S Army, on leave from Yale University and John B Pierce Laboratory of Hygiene* (1, 1939)
- Galambos, Robert, M A, Ph D Psycho-Acoustic Laboratory, Memorial Hall, Cambridge 38, Mass (1, 1942)
- Gall, Edward A, M D Bethesda Hospital, Cincinnati, O *Assistant Professor of Pathology, College of Medicine, University of Cincinnati* (4, 1941)
- Gallagher, Thomas F, Ph D Sloan-Kettering Institute, 444 E 68th St, New York 21, N Y *Member* (2, 1932)
- Gallup, Willis D, M S, Ph D Oklahoma Agricultural and Mechanical College, Stillwater *Chemist and Professor of Agricultural Chemistry* (2, 1932)
- Gamble, James L, M D, S M 33 Edgehill Rd, Brookline, Mass *Professor of Pediatrics, Harvard Medical School* (2, 1922, 5, 1933)
- Gantt, W Horsley, M D Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore, Md *Associate in Psychiatry* (1, 1935)



- Garbat, Abraham L, M D 103 E 78th St, New York City *Attending Physician, Lenox Hill Hospital* (6, 1913)
- Garner, Raymond L, Ph D 218 West Medical Building, University of Michigan, Ann Arbor, Mich *Assistant Professor* (2, 1917)
- Garrey, Walter Eugene, Ph D, M D Vanderbilt University School of Medicine, Nashville, Tenn *Professor Emeritus of Physiology* (1, 1910, 2, 1906)
- Gasser, Herbert S, A M, M D, Sc D (hon) Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Director of Laboratories, Member of the National Academy of Sciences* (1, 1915, 3, 1924)
- Gassner, Frank A, M S, D V M Colorado A and M College, Fort Collins *Associate Professor of Physiology, Colorado State College, Associate Pathologist, Colorado State Experiment Station* (1, 1947)
- Gates, Olive, M D 25 Shattuck St, Boston, Mass *Associate Pathologist* (4, 1940)
- Gaunt, Robert, Ph D Syracuse University, Syracuse, N Y *Professor and Chairman of the Department of Zoology* (1, 1939)
- Gay, Leslie N, M D 1114 St Paul St, Baltimore, Md *Director of the Allergy Clinic, Johns Hopkins Hospital, Visiting Physician to Johns Hopkins Hospital, Associate in Medicine, Johns Hopkins University* (6, 1927)
- Geiling, E M K, M S, M D, Ph D University of Chicago, Chicago, Ill *Frank P Hixon Distinguished Service Professor of Pharmacology and Chairman of Department* (1, 1933, 2, 1927, 3, 1925)
- Gelfan, Samuel, Ph D Yale University School of Medicine, 333 Cedar St, New Haven 11 Conn *Assistant Professor of Physiology* (1, 1930)
- Gellhorn, Alfred, M D Dept of Pharmacology, College of Physicians and Surgeons, 630 West 168th St, New York, 32, N Y *Associate Professor of Pharmacology* (3, 1946)
- Gellhorn, Ernst, M D, Ph D Room 116, Medical Sciences, University of Minnesota, Minneapolis *Professor of Neurophysiology* (1, 1930)
- Gemmell, Chalmers L, M D Department of Pharmacology, Medical School University of Virginia, Charlottesville *Professor of Pharmacology* (1, 1928, 2, 1935, 3, 1946)
- Gerard, R W, Ph D, M D University of Chicago, Chicago, Ill *Professor of Physiology* (1, 1927)
- Gersh, Isadore, M D College of Medicine University of Illinois, 1853 Polk St, Chicago 12, Ill *Associate Professor of Pathology* (4, 1947)
- Gerstenberger, Henry John, M D Western Reserve University, Cleveland, O *Professor Emeritus of Pediatrics, School of Medicine, Western Reserve University, Director of Pediatrics, Babies and Children's Hospital* (5, 1938)
- Gesell, Robert, M D University of Michigan, Ann Arbor *Professor of Physiology* (1, 1913)
- Gettler, Alexander O, A M, Ph D, LL D New York University, 29 Washington Place, New York City *Professor of Chemistry and Toxicology, Toxicologist to Chief Medical Examiner's Office* (2, 1916)
- Gey, George Otto, M D Division for Cellular Pathology, Room 531, Dispensary Building, Johns Hopkins Hospital and University, Baltimore 5, Md *Instructor in Surgery* (1, 1940)
- Gibbs, Frederick Andrews, M D 720 N Michigan Ave, Suite 610, Chicago, Ill (1, 1935)
- Gibbs, Owen Stanley, M B, Ch B (Edin), M D P O Box 166, Whitehaven, Tenn *Research Consultant* (1, 1935, 3, 1930)
- Gibson, Robert Banks, Ph D University Hospital, Iowa City, Iowa *Associate Professor of Biochemistry, State University of Iowa* (1, 1907, 2, 1906)
- Gies, William John, M S, Ph D, Sc D, LL D, F A C D 632 W 168th St, New York City *Professor of Biological Chemistry, Columbia University* (1, 1898, 2, 1906, 3, 1909)
- Gilbert, Ruth, A M, M D R F D 2, Altamont, N Y *Bacteriologist, New York State Department of Health, Albany* (6, 1920)
- Gilman, Alfred, Ph D College of Physicians and Surgeons, 630 West 168th St, New York 32, N Y *Associate Professor of Pharmacology* (1, 1935, 3, 1934)
- Gilson, Arthur S, Jr, A M, Ph D Washington University Medical School, St Louis, Mo *Associate Professor of Physiology* (1, 1927)
- Githens, Thomas Stotesbury, M D The Cambridge Alden Park, Wissahickon and School Lane, Germantown, Philadelphia, Pa (1, 1915)
- Givens, Maurice H, Ph D Box 3836, Peninsula Station, Daytona Beach, Fla (1, 1917, 2, 1915)
- Glaser, O C, Ph D Amherst College, Amherst, Mass *Professor of Biology* (1, 1913)
- Glass, Howard G, M S, Ph D Department of Pharmacology, Marquette University School of Medicine, 561 N 15th Street, Milwaukee 3, Wis *Instructor* (3, 1947)
- Glazko, Anthony J, Ph D Box 255, Detroit 31, Mich *Research Laboratories, Parke, Davis & Co Research Chemist* (1, 1942)
- Glick, David, Ph D 225 Medical Sciences Building, University of Minnesota, Minneapolis 14, Minn *Associate Professor of Physiological Chemistry and Consultant to Veteran's Hospital* (2, 1936)
- Glickman, Nathaniel, M S Department of Medicine, University of Illinois College of Medicine, 1853 W Polk St, Chicago 12, Ill *Physiologist in the Aero Medical and Atmospheric Environment Unit* (1, 1947)
- Goebel, Walther F, Ph D The Rockefeller In-

- stitute for Medical Research, 66th St and York Ave, New York City *Member* (2, 1929, 6, 1937)
- Goerner, Alfred, Ph G, Phaim D, M D 366 Sterling Place, Brooklyn, N Y *Assistant Clinical Professor of Medicine Long Island College of Medicine* (2, 1939)
- Goettsch, Marianne, Ph D School of Tropical Medicine of Columbia University, San Juan, Puerto Rico *Assistant Professor of Chemistry* (2, 1933, 5, 1941)
- Goetzi, Franz R, Ph D, M D Department of Medical Research, The Permanente Foundation, Oakland 11, Calif *Director* (1, 1947)
- Gold, Harry, M D 1300 York Ave, New York City *Assistant Professor of Pharmacology, Cornell Medical College* (3, 1927)
- Goldblatt, Harry, M D Director Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif (1, 1945, 4, 1927)
- Golden, Alfred, M D Baptist Memorial Hospital, 889 Madison Avenue, Memphis, Tenn *Director of Laboratories, University of Tennessee School of Medicine, Associate Professor of Pathology* (4, 1947)
- Goldfarb, Walter, M D 105 W 55th St, New York, N Y (1, 1938)
- Goldforb, A J, Ph D College of the City of New York, New York City *Professor of Biology* (1, 1930)
- Goldie, Horace, M D, D T M Nanuet, N Y *City of New York, Dept of Health* (6, 1943)
- Goldring, William, M D New York University College of Medicine, 477 First Ave, New York City *Associate Professor of Medicine* (1, 1939)
- Goldschmidt, Samuel, Ph D University of Pennsylvania Medical School, Philadelphia *Associate Professor of Physiology* (1, 1919, 2, 1915)
- oldsmith, Grace A Tulane University of Louisiana, New Orleans (5, 1943)
- Golub, Orville Joseph, M S, Ph D Lt Cmdr HS, USNR, Camp Detrick, Frederick, Md *Research Bacteriologist (Viruses)* (6, 1944)
- Goodman, Louis Sanford, M S, M D University of Utah School of Medicine, Salt Lake City *Professor of Pharmacology and Chairman of the Department of Pharmacology* (1, 1946, 3, 1937)
- Goodner, Kenneth, Ph D Jefferson Medical College, Philadelphia, Pa *Professor of Bacteriology* (6, 1932)
- Goodpasture, Ernest William, M D Vanderbilt University Medical School, Nashville, Tenn *Professor of Pathology and Dean* (4, 1923)
- Gordon, Albert S, M S, Ph D Washington Square College of Arts and Sciences, New York University, New York City *Associate Professor of Biology* (1, 1942)
- Gordon, Francis B, M D University of Chicago 5724 Ellis Avenue, Chicago, Ill *Associate Professor of Bacteriology* (4, 1917)
- Gordon, Harry H, M D 1200 E 9th Ave, Denver, Colo *Professor of Pediatrics, University of Colorado Medical School, Pediatrician in Chief, Colorado General Hospital* (5, 1910)
- Gordon, Irving, M D Division of Laboratories & Research, N Y State Dept of Health, New Scotland Ave, Albany 1, N Y *Senior Medical Bacteriologist* (6, 1943)
- Gordon, William G, M A, Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Philadelphia 18, Pa *Senior Chemist* (2, 1939)
- Gortner, Ross Aiken, Jr, M S, Ph D Shanklin Laboratory, Wesleyan University, Middletown, Conn *Associate Professor of Biochemistry* (5, 1917)
- Gortner, Willis A, Ph D Cornell University School of Nutrition, Ithaca, N Y *Associate Professor of Biochemistry* (2, 1917)
- Goss, Harold, Ph D University of California College of Agriculture, Davis *Professor of Animal Husbandry* (2, 1936, 5, 1933)
- Goth, Andres, M D Southwestern Medical College, 2211 Oak Lawn Avenue, Dallas 4, Tex *Associate Professor of Pharmacology* (3, 1947)
- Gottschall, Russell Y, M S, Ph D Bureau of Laboratories, Michigan Department of Health, Lansing *Bacteriologist* (6, 1939)
- Goudsmit, Arnoldus, Jr, M D, Ph D 40 Roberts Avenue, Glenside, Pa *Associate in Clinical Physiology, Jeanes Hospital, Fox Chase, Philadelphia 11, Pa* (1, 1940)
- Govier, William M, M D The Upjohn Co, Kalamazoo 99, Mich *Research Division* (3, 1944)
- Grabfield, G Philip, M D 27 Forest St, Milton, Mass *Associate in Medicine and Pharmacology, Harvard Medical School (At present on leave of absence, Col M C, U S A)* (3, 1923)
- Grady, Hugh G, M D Jefferson Medical College, Philadelphia, Pa *Assistant Professor of Pathology* (4, 1940)
- Graef, Irving, M D 360 East 55th, New York, N Y New York University College of Medicine *Assistant Professor of Clinical Medicine, Associate Visiting Physician, 3rd (N Y U) Medical Division, Bellevue Hospital, Adjunct Physician, Lenox Hill Hospital* (4, 1941)
- Graham, Clarence H, Ph D Columbia University, New York 27, N Y *Professor of Psychology* (1, 1933)
- Graham, Helen Tredway, A M, Ph D Euclid Ave and Kingshighway, St Louis, Mo *Associate Professor of Pharmacology, Washington University School of Medicine* (1, 1933, 3, 1931)

- Grant, R Lorimer, M S, Ph D Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D C *Pharmacologist* (2, 1938)
- Graubard, Mark, M A, Ph D Dept of Physiology, University of Minnesota, Minneapolis (1, 1940)
- Grauer, Robert C, M D Allegheny General Hospital, Pittsburgh, Pa *Head of Department of Research in Endocrinology and Metabolism, William H Singer Memorial Research Laboratory, Lecturer in Pathology and Instructor in Medicine, School of Medicine, University of Pittsburgh* (4, 1941)
- Gray, John S, M S, Ph D M D Northwestern Univ Medical School, 303 E Chicago Ave, Chicago 11, Ill *Professor of Physiology and Chairman of Department* (1, 1937)
- Gray, M Geneva, M A, Ph D Laboratories of Arthur D Little, Inc, Cambridge, Mass *Director Pharmacological Research* (3, 1946)
- Gray, Samuel H, M D The Jewish Hospital of St Louis, Kingshighway and Forest Park Blvd, St Louis, Mo *Director of Laboratories, Jewish Hospital, Associate Professor of Pathology, Washington University* (1, 1939)
- Greaves, J D, M S, Ph D Western Regional Research Lab, U S Dept of Agriculture, 800 Buchanan St, Albany 6, Calif *Biochemist* (2, 1938)
- Greaves, Joseph E, Ph D Utah State Agricultural College, Logan *Professor and Head of Department of Bacteriology and Biochemistry* (2, 1940)
- Greeley, Paul O, A M, Ph D, M D University of Southern California Medical School, University Park, Los Angeles *Dept of Aviation Medicine* (1, 1940)
- Green, Arda Alden, M D Cleveland Clinic, Euclid and E 93rd St, Cleveland 6, O *Research Division* (2, 1932)
- Green, Daniel M, M D, M S Dept of Medicine, University of Washington School of Medicine, Seattle 5 *Chief, Section of Experimental Medicine and Therapeutics* (3, 1942)
- Green, David E, Ph D Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 W 168th St New York 32, N Y *Associate Professor of Biochemistry* (2, 1941)
- Green, Harold David, M D Bowman Gray School of Medicine, Wake Forest College, Winston-Salem 7, N C *Professor of Physiology and Pharmacology* (1, 1936, 3, 1945)
- Greenberg, David Morris, Ph D University of California, Berkeley *Professor of Biochemistry, Chairman of Division* (2, 1927, 5, 1946)
- Greenberg, Louis D, Ph D Univ of Calif Medical Center, 3rd and Parnassus Aves, San Francisco 22, Calif *Assistant Professor of Pathology and Pharmacology* (2, 1916)
- Greene, Carl Hartley, Ph D, M D 140 E 54th St., New York City *Associate Professor of Clinical Medicine, New York Post Graduate Medical School of Columbia University, Clinical Professor of Medicine, Long Island College of Medicine* (1, 1921, 2, 1922, 4, 1924)
- Greene, Harry S N, M D, C M Department of Pathology, Yale University School of Medicine, New Haven, Conn *Professor of Pathology* (4, 1937)
- Greene, James Alexander, M D Baylor University, College of Medicine, Buffalo Drive, Houston, Texas *Professor and Chairman of the Department of Internal Medicine and Dean of the Clinical Faculty* (1, 1939)
- Greene, Ronald R, M S, M D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Instructor in Physiology, Instructor in Obstetrics and Gynecology* (1, 1941)
- Greengard, Harry, Ph D, M D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Assistant Professor of Physiology* (1, 1939)
- Greenstein, Jesse P, Ph D National Cancer Institute, Bethesda, Md *Chief Biochemist* (2, 1935)
- Greenwald, Isidor, Ph D 477 First Ave, New York City *Associate Professor of Chemistry, New York University College of Medicine* (2, 1912, 5, 1933)
- Greep, Roy O, Ph D Harvard School of Dental Medicine, 188 Longwood Ave, Boston 15, Mass *Assistant Professor of Dental Science (Dental Medicine), Teaching Fellow in Anatomy (Medical School)* (1, 1940)
- Greer, C M, M S Vanderbilt University School of Medicine, Nashville, Tenn *Research Associate in Pharmacology* (3, 1938)
- Gregersen, Magnus I, A M, Ph D College of Physicians and Surgeons, Columbia University, 630 W 168th St, New York City *Professor of Physiology* (1, 1933)
- Gregg, Donald Eaton, M S, Ph D, M D Armored Medical Research Laboratory, Fort Knox, Ky *Chief Research Physician* (1, 1933)
- Gregory, Raymond L, Ph D, M D University of Texas School of Medicine, 1419—24th St., Galveston *Professor of Medicine* (1, 1945)
- Greig, Margaret E, B A, M A, Ph D Vanderbilt Univ School of Medicine, Nashville 4, Tenn *Assistant Professor in Pharmacology* (3, 1946)
- Greisheimer, Esther M, Ph D, M D Temple University Medical School, 3400 N Broad St, Philadelphia, Pa *Professor of Physiology* (1, 1925)
- Grenell, Robert G, Ph D Section of Neuroanatomy, Yale University School of Med, New

- Haven 11, Conn *Research Assistant (rank of Instructor), Laboratory of Physiology* (1, 1945)
- Griffin, Angus, Ph D Department of Bacteriology, George Washington University School of Medicine, 1335 H St., N W, Washington, D C *Assistant Professor of Bacteriology* (6, 1940)
- Griffith, Fred R., Jr., M A, Ph D 24 High St., Buffalo, N Y *Professor of Physiology, University of Buffalo Medical School* (1, 1923, 5, 1933)
- Griffith, Wendell H., M S, Ph D St Louis Univ School of Medicine, St Louis 4, Mo *Professor of Biological Chemistry* (2, 1923, 5, 1931)
- Grimson, Keith S., M D Duke University School of Medicine, Durham, N C *Associate Professor of Surgery* (1, 1943)
- Grindlay, John H., M D Mayo Clinic, Rochester, Minn (1, 1945)
- Groat, Richard A., Ph D Bowman Gray School of Medicine, Winston Salem 7, N C *Assistant Professor of Anatomy* (1, 1945)
- Groat, William A., M D 713 E Genesee St., Syracuse, N Y *Professor of Clinical Pathology, Syracuse University College of Medicine* (6, 1917)
- Grodins, Fred S., Ph D M D Northwestern University Medical School, 303 E Chicago Ave., Chicago 11, Ill *Associate Professor of Physiology* (1, 1945)
- Grollman, Arthur, M D, Ph D Southwestern Medical College, 2211 Oak Lawn Ave., Dallas, Texas *Professor of Medicine and Chairman of the Department of Experimental Medicine, Professor of Pharmacology and Chairman of the Department of Physiology and Pharmacology* (1, 1928, 3, 1933)
- Gross, Erwin G., Ph D, M D Medical Laboratories, State University of Iowa, Iowa City *Professor of Pharmacology* (1, 1927, 2, 1923, 3, 1927)
- Robert E., M D Harvard Medical School, 300 Longwood Ave., Boston, Mass *Ladd Professor of Children's Surgery* (4, 1940)
- Grossman, Morton Irvin, M S, Ph D, M D, University of Illinois College of Medicine, Chicago 12 *Assistant Professor of Physiology* (1, 1946)
- Gruber, Charles M., A M, M D, Ph D Jefferson Medical College, 1025 Walnut St., Philadelphia, Pa *Professor of Pharmacology* (1, 1914, 3, 1919)
- Gruhzit, Oswald M., M D Research Laboratories, Parke, Davis & Co., Detroit, Mich *Research in Pathology and Pharmacology* (4, 1928)
- Grundfest, Harry, A M, Ph D Columbia Univ P and S, 630 West 168th St., New York 32, N Y *Associate in Neurology* (1, 1932)
- Gudernatsch, F., Ph D Graduate School, New York University, Washington Square E., New York City *Visiting Professor* (1, 1930)
- Guerra, Francisco, M Sc, Med Major, D Litt M D Facultad de Medicina, Universidad Nacional de Mexico, Mexico D F *Professor of Pharmacology* (3, 1947)
- Guerrant, N B., M S, Ph D Pennsylvania State College, State College *Professor of Biological Chemistry* (2, 1934, 5, 1933)
- Guest, George Martin, M S, M D The Children's Hospital, Research Foundation, Elland and Bethesda Aves., Cincinnati, O *Fellow of the Children's Hospital Research Foundation, Associate Professor of Pediatrics, University of Cincinnati, College of Medicine and Graduate School* (2, 1933)
- Guest, Maurice Mason, Ph D Dept of Physiology, Wayne Univ., College of Medicine, Detroit 26, Mich *Associate Professor of Physiology* (1, 1916)
- Gulick, Addison, A M, Ph D 308 Westmount Ave., Columbia, Mo *Professor of Physiological Chemistry, University of Missouri* (1, 1915, 5, 1933)
- Gunn, Francis D., M D University of Utah, School of Medicine, Salt Lake City *Professor of Pathology* (1, 1933)
- Gunsalus, Irwin C., Ph D Bacteriology Department, Indiana University, Bloomington *Associate Professor of Bacteriology* (2, 1916)
- Gurin, Samuel, Ph D University of Pennsylvania School of Medicine, Philadelphia *Professor* (2, 1938)
- Gustavson, Reuben G., Ph D University of Nebraska, Lincoln *Chancellor* (2, 1927)
- Gustus, Edwin L., M Sc, Ph D 6744 S Ridgeland Ave., Chicago 49, Ill *Research Consultant, Research and Development Branch, Office of the Quartermaster General, Washington, D C* (2, 1934)
- Guthrie, Charles Claude, M D, Ph D, Sc D University of Pittsburgh Medical School, Pittsburgh, Pa *Professor of Physiology and Pharmacology* (1, 1905, 3, 1909)
- Gutman, Alexander B., M A, Ph D, M D Presbyterian Hospital, 622 West 168 Street, New York 32, N Y *Assistant Professor of Medicine, Columbia University College of Physicians and Surgeons* (2, 1947)
- Guttman, Rita M., M A, Ph D Brooklyn College, Brooklyn, N Y *Instructor in Physiology* (1, 1946)
- Gyorgy, Paul, M D 3400 Spruce St., Philadelphia 4, Pa *Professor of Clinical Pediatrics, University of Pennsylvania School of Medicine* (2, 1938, 5, 1939)
- Haag, Harvey B., M D Medical College of Virginia, Richmond *Professor of Pharmacology* (3, 1934)

- Haag, J R, Ph D Oregon Agricultural Experiment Station, Corvallis *Chemist* (2, 1917, 5, 1941)
- Haas, Erwin, Ph D Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles 27, Calif *Research Associate* (2, 1916)
- Haas, George, M D Presbyterian Hospital of Chicago, 1753 W Congress St, Chicago 12, Ill *Professor of Pathology, Univ of Illinois College of Medicine Chairman of Dept of Pathology, Presbyterian Hospital of Chicago* (4, 1939)
- Haberman, Sol, M A, Ph D Wm Buchanan Blood, Plasma and Serum Center, Baylor Hospital, Dallas, Texas *Chief of Bacteriology and Serology Services* (6, 1944)
- Hadidian, Zareh, Ph D Worcester Foundation for Experimental Biology, Shrewsbury, Mass *Associate Fellow* (1, 1945)
- Hadley, Philip Bardwell, Ph D Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh *Chief of Bacteriological Service and Research Bacteriologist* (4, 1927)
- Hafkesbring, H Roberta, Ph D Woman's Medical College of Pennsylvania, East Falls, Philadelphia *Professor of Physiology* (1, 1931)
- Haggard, Howard W, M D 4 Hillhouse Ave, New Haven, Conn *Director of the Laboratory of Applied Physiology, Yale University* (1, 1919, 2, 1920)
- Hahn, Paul F, Ph D Vanderbilt University School of Medicine, Nashville, Tenn *Associate Professor of Biochemistry* (1, 1946, 4, 1939)
- Hag, Charles, M A, Ph D New York Medical College, Fifth Ave at 105th St, New York City *Associate Professor of Physiology and Biochemistry* (1, 1942)
- Haist, Reginald E, M A, M D, Ph D University of Toronto, Toronto, Ontario, Canada *Associate Professor of Physiology* (1, 1943)
- Halbert, Seymour P, M D School of Public Health, University of North Carolina, Chapel Hill, N C *Assistant Professor, Experimental Medicine* (6, 1947)
- Haldi, John, A M, Ph D Emory University, Emory University, Ga (1, 1928)
- Hale, Wm M, M D The State University of Iowa College of Medicine, Iowa City *Professor of Bacteriology* (4, 1941, 6, 1935)
- Hale, Worth, M D Antrim, New Hampshire (1, 1908, 3, 1908)
- Hall, F G, M A, Ph D Duke Univ School of Medicine, Dept of Physiology and Pharmacology, Durham, N C (1, 1937)
- Hall, George Edward, M D, Ph D University of Western Ontario, Ottawa Ave and Waterloo St, London, Canada *Dean of the Faculty of Medicine* (1, 1938)
- Hall, Victor E, M A, M D Department of Physiology, Stanford University, Calif *Professor of Physiology* (1, 1934)
- Hallenbeck, George Aaron, Ph D, M D Mayo Clinic, Rochester, Minn *Research Associate* (1, 1916)
- Halliday, Nellie, Ph D University of California Hospital, San Francisco 22 Calif (5, 1933)
- Halpert, Bela, M D University of Oklahoma School of Medicine, Oklahoma City *Director of Laboratories and Professor of Clinical Pathology* (4, 1936)
- Halsey, John T, M D P O Box 264, Waveland, Miss *Professor Emeritus of Pharmacology, Tulane University of Louisiana* (3, 1929)
- Halstead, Ward C, M A, Ph D Dept of Medicine, University of Chicago, Chicago, Ill *Associate Professor Experimental Psychology, Division of Psychiatry* (1, 1942)
- Ham, Arthur W, M B University of Toronto, Toronto 5, Canada *Professor of Anatomy, in charge of Histology* (4, 1939)
- Hambourger, Walter E, Ph D, M D G D Searle & Co, P O Box 5110, Chicago, Ill *Chief Pharmacologist* (3, 1934)
- Hamilton, Bengt L K, M D U S Marine Hospital, Staten Island 4, N Y *Senior Surgeon (R), U S Public Health Service* (2, 1925)
- Hamilton, James B, Ph D Department of Anatomy, Long Island College of Med, 350 Henry Street, Brooklyn 2, N Y (1, 1938)
- Hamilton, Paul B, M A, Ph D Alfred I Dupont Institute, Nemours Foundation, Rockland Rd, Wilmington 99, Del *Chief of Biochemistry* (2, 1946)
- Hamilton, Tom S, M S, Ph D 551 Davenport Hall, University of Illinois, Urbana *Professor and Chief in Animal Nutrition* (2, 1937, 5, 1938)
- Hamilton, W F, Ph D University of Georgia School of Medicine, Augusta *Professor of Physiology and Pharmacology* (1, 1924)
- Hammatt, Frederick S, M S, A M, Ph D 493 Commercial St, Provincetown, Mass (1, 1920, 2, 1917)
- Hammon, William McD, M D, M P H, Dr P H 104 Lunado Way, San Francisco 12, Calif *Professor of Epidemiology, Univ of Calif School of Public Health, and Professor of Epidemiology, George Williams Hooper Foundation* (4, 1944)
- Hampel, C W, Ph D New York University College of Medicine, New York, N Y *Visiting Professor of Physiology and Anatomy* (1, 1936)
- Hand, David B, Ph D New York State Agricultural Experiment Station, Geneva, New York *Head, Division of Food Science and Technology* (2, 1947)
- Handler, Philip, M S, Ph D Duke University School of Medicine, Durham, N C *Associate*

- Professor of Biochemistry and Nutrition* (2, 1944, 5, 1946)
- Handley, Carroll A**, Ph D Baylor Univ College of Medicine, Houston 1, Texas *Professor of Physiology and Pharmacology* (3, 1942)
- Haney, Hance F**, Ph D, M D University of Oregon Medical School, Portland *Professor of Physiology and Head of the Department* (1, 1939)
- Hanger, Franklin**, M D College of Physicians and Surgeons, 630 W 168th St, New York City *Associate Professor of Medicine, Columbia University* (6, 1930)
- Hanke, Martin E**, Ph D University of Chicago, Chicago, Ill *Associate Professor of Biochemistry* (2, 1925)
- Hanke, Milton Theo**, Ph D 7550 S Green St, Chicago, Ill *Research Consultant, Biochemistry and Nutrition* (2, 1919)
- Hanks, John H**, Ph D Culion, Palawan, Philippine Islands (6, 1935)
- Hansen, Arild E**, M D University of Texas Medical School, Galveston *Professor of Pediatrics and Chairman of the Department, Director of the University of Texas Child Health Program* (4, 1941, 5, 1942)
- Hanzal, Ramon F**, M A, Ph D Killian Research Laboratories, 49 W 45th St, New York City *Biochemist* (2, 1935)
- Hanzlik, Paul J**, M D School of Medicine, Stanford University, Sacramento and Webster Sts, San Francisco, Calif *Professor of Pharmacology* (1, 1912)
- Hardy, James Daniel**, A M, Ph D Russell Sage Institute of Pathology, 525 E 68th St, New York City *Research Associate* (1, 1939)
- Hardy, Mary**, D Sc The Brearley School, 610 E 83rd St, New York City *Teacher of Science* (1, 1933)
- Hare, Kendrick**, Ph D 1300 York Ave, New York, N Y (1, 1938)
- ger, R N**, M A, Ph D Indiana University School of Medicine, Indianapolis *Professor of Biochemistry and Toxicology* (2, 1938)
- Harkins, Henry Nelson**, M S, Ph D, M D Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Surgery, Johns Hopkins University Medical School* (1, 1942)
- Harmon, Paul M**, A M, Ph D Indiana University, Bloomington *Professor of Physiology* (1, 1930)
- Harne, O G** University of Maryland School of Medicine, Baltimore *Associate Professor of Histology* (1, 1935)
- Harned, Ben King**, M S, Ph D Lederle Laboratories, Pearl River, N Y *Research Pharmacologist* (2, 1931, 3, 1941)
- Harris, Albert H**, M D, N Y State Dept of Health, Division of Laboratories and Research, New Scotland Ave, Albany 1, N Y *Associate Bacteriologist* (6, 1937)
- Harris, Albert Sidney**, Ph D College of Medicine, Baylor University, Houston 5, Texas (1, 1939)
- Harris, Milton**, Ph D 1246 Taylor St, N W, Washington 11, D C *President, Harris Research Laboratories* (2, 1939)
- Harris, Philip L**, M S, Ph D Distillation Products, Inc, 755 Ridge Road W, Rochester 13, N Y *Head of Biochemistry Research Department, and Instructor in Physiology, University of Rochester Medical School* (5, 1915, 2, 1916)
- Harris, Robert S** Massachusetts Institute of Technology, Cambridge *Professor of Nutritional Biochemistry* (5, 1911)
- Harris, S C**, M S, Ph D Department of Physiology and Pharmacology, Northwestern University, Chicago, Ill *Chairman of Department* (1, 1917)
- Harris, T N**, M D, 2222 N 53rd St, Philadelphia 31, Pa *Associate in Pediatrics, Univ of Pennsylvania* (6, 1916)
- Harris, William H**, M D Tulane University School of Medicine, New Orleans, La *Assistant Professor of Pathology and Bacteriology* (4, 1925)
- Harrison, Frank**, M S, Ph D University of Tennessee College of Medicine, Memphis *Professor and Chief, Division of Anatomy* (1, 1911)
- Harrison, James A**, Ph D Temple Univ, Philadelphia 22, Pa *Professor of Biology* (6, 1916)
- Harrison, Ross Granville**, M D, Ph D, Sc D Osborn Zoological Laboratory, New Haven, Conn *Sterling Professor of Biology, Emeritus, Yale University, Chairman of the National Research Council, Member of the National Academy of Sciences* (1, 1906)
- Harrison, R Wendell**, M D, Ph D 950 East 59th St, Chicago 37, Ill *Professor of Bacteriology, Dean, Division of Biological Sciences, Univ of Chicago* (6, 1934)
- Harrow, Benjamin M**, Ph D College of the City of New York, Convent Ave and 139th St, New York City *Professor of Chemistry* (2, 1927)
- Hart, E B**, B S Agricultural College, Madison, Wis *Professor of Biochemistry, University of Wisconsin* (2, 1910, 5, 1933)
- Hart, E Ross**, M S, Ph D Jefferson Medical College, 1025 Walnut St, Philadelphia, Pa *Assistant Professor of Pharmacology* (3, 1944)
- Hart, William M**, Ph D Temple Medical School, Broad and Ontario Sts, Philadelphia 40, Pa *Assistant Professor of Physiological Chemistry* (1, 1945)
- Hartline, H K**, M D Johnson Foundation University of Pennsylvania Hospital, Philadel-

- Phillips, P., Assistant Professor of Biophysics, (1, 1929)
- Hartman, Carl G., A M., Ph D Department of Zoology, University of Illinois, Urbana Professor of Zoology and Head of the Department, Member, National Academy of Sciences (1, 1921)
- Hartman, Frank Alexander, A M., Ph D Department of Physiology, Ohio State University, Columbus Professor of Physiology and Chairman of the Department (1, 1916)
- Hartman, F W., M D Henry Ford Hospital, Detroit, Mich Pathologist (4, 1927)
- Hartmann, Alexis F., M S., M D 500 S Kingshighway, St Louis, Mo Professor of Pediatrics, Washington University School of Medicine (2, 1932)
- Harvey, A McGhee, A B., M D Johns Hopkins Hospital, Baltimore 5, Md Professor of Medicine, Johns Hopkins Univ Medical School, Physician-in-chief, Johns Hopkins Hospital (1, 1946, 3, 1946)
- Harvey, E Newton, Ph D Guyot Hall, Princeton, N J Henry Fairfield Osborn Professor of Biology, Princeton University, Member, National Academy of Sciences (1, 1914, 2, 1916)
- Hassid, William Z., M S., Ph D Division of Plant Nutrition, Univ of California, Berkeley, Calif Professor of Plant Nutrition (2, 1946)
- Hastings, A Baird, Ph D., Sc D Harvard Medical School, Boston, Mass Hamilton Kuhn Professor of Biological Chemistry, Member, National Academy of Sciences (1, 1927, 2, 1921, 5, 1940)
- Haterius, Hans O., Ph D Boston University School of Medicine, 80 D Concord St., Boston 18, Mass Professor of Physiology (1, 1936)
- Hathaway, Milicent L., M A., Ph D Bureau of Human Nutrition and Home Economics, (Food and Nutrition Division), Agricultural Research Administration, Washington 25, D C (5, 1945)
- Hauck, Hazel M., Ph D Cornell University, Ithaca, N Y Professor of Home Economics (5, 1941)
- Hauge, Siegfried M., Ph D Purdue University Agricultural Experiment Station, Lafayette, Ind Research Associate in Biochemistry (5, 1933)
- Haury, Victor G., M B., M D 1428 S Willow St., Ottawa, Kansas (3, 1939)
- Haven, Frances L., M A., Ph D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N Y Associate in Biochemistry (2, 1941)
- Hawk, Philip B., M S., Ph D Food Research Laboratories, 48-14 33rd St., Long Island City N Y President (1, 1903, 2, 1906)
- Hawkins, J E., Jr., B A (Oxon), Ph D Merck Institute for Therapeutic Research, Rahway, N J Physiologist (1, 1943)
- Hawkins, William Bruce, M D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N Y Associate Professor of Pathology (4, 1933)
- Hawley, Estelle E., Ph D Medical School, University of Rochester, Rochester, N Y Research Fellow in Pediatrics (5, 1935)
- Hay, Eleanor Clarke, Ph D 7 Greenhill Rd., Madison, N J (1, 1945)
- Hayman, J M., Jr., M D Lakeside Hospital, Cleveland, O Professor of Clinical Medicine and Therapeutics, Western Reserve University (1, 1928, 3, 1932)
- Haynes, Florence W., M A., Ph D Harvard Medical School, 25 Shattuck St., Boston, Mass Research Fellow in Medicine (1, 1937)
- Hays, Edwin Everett, M S., Ph D The Armour Laboratories, 1425 W 42nd St., Chicago 9, Ill Section Head of Biochemical Research (2, 1946)
- Haythorn, Samuel R., M D Allegheny General Hospital, 320 E North Ave., Pittsburgh, Pa Director of William H Singer Memorial Laboratory (4, 1925)
- Haywood, Charlotte, A M., Ph D Mount Holyoke College, South Hadley, Mass Professor of Physiology (1, 1939)
- Hazen, Elizabeth L., M A., Ph D New York State Department of Health Laboratories, 339 E 25th St., New York City Senior Bacteriologist (6, 1931)
- Hazelton, Lloyd W., Ph D Box 333, Falls Church, Va Research Consultant (3, 1944)
- Hechter, Oscar M., Ph D Worcester Foundation Exper Biol., 222 Maple Ave., Shrewsbury, Mass (1, 1945)
- Heft, Hattie L., Ph D Teachers College, Columbia University, New York City Assistant Professor of Physiological Chemistry (2, 1927)
- Hegnauer, Albert H., Ph D Syracuse University, Syracuse, N Y Assistant Professor of Physiology (1, 1937)
- Hegsted, David Mark, M S., Ph D Schools of Medicine & Public Health, Harvard University, 25 Shattuck St., Boston, Mass Assistant Professor of Nutrition (5, 1944)
- Heidelberger, Michael, Ph D, M A 620 W 168th St., New York City Professor of Biochemistry, Columbia University, Chemist to the Medical Service, Presbyterian Hospital (2, 1927, 6, 1935)
- Heilbrunn, Lewis Victor, Ph D University of Pennsylvania, Philadelphia Professor of Zoology (1, 1930)
- Heim, J William, Ph D 1 Yale Ave., Dayton 6, Ohio Aero Medical Laboratory, Army Air Forces, Wright Field Principal Research Phys-



- ologist, Assistant in Physiology, Harvard School of Public Health (1, 1936)
- Heinbecker, Peter, M D Washington University Medical School, St Louis, Mo Associate Professor of Clinical Surgery (1, 1930)
- Helff, O M, M S, Ph D New York University, University Heights, New York City Associate Professor of Biology (1, 1932)
- Hellbaum, Arthur A, M A, Ph D, M D University of Oklahoma School of Medicine, Oklahoma City Professor of Pharmacology and Physiology (1, 1937, 3, 1945)
- Hellebrandt, Frances Anna, M D Medical College of Virginia, Richmond Professor of Physical Medicine (1, 1933)
- Heller, Carl G, M D, Ph D University of Oregon Medical School, Portland 1 Associate Professor of Physiology and Medicine (1, 1915)
- Heller, Victor G, Ph D Oklahoma A & M College, Stillwater Head of the Department of Agricultural Chemistry Research (2, 1935, 5, 1935)
- Hellerman, Leslie, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore 5, Md Associate Professor of Physiological Chemistry (2, 1935)
- Helmer, Osear Marvin, M S, Ph D Lilly Laboratory for Clinical Research, The Indianapolis City Hospital, Indianapolis, Ind Head of Department of Physiological Chemistry (2, 1935)
- Hemingway, Allan, Ph D 241 Cecil St, S E, Minneapolis Associate Professor of Physiology, University of Minnesota (1, 1933)
- Hendrix, Byron M, Ph D School of Medicine, University of Texas, Galveston Professor of Biochemistry (2, 1920)
- Hendrix, James Paisley, B S, M A, M D Duke Hospital, Durham, N C Associate in Medicine (in charge of Therapeutics), Associate in Physiology and Pharmacology, Duke University School of Medicine (3, 1942)
- Hendry, Jessie L, M A Division of Laboratories and Research, New York State Department of Health, New Scotland Ave, Albany Senior Bacteriologist (6, 1938)
- Henle, Werner, M D 1740 Bainbridge St, Philadelphia 46, Pa Associate Professor of Virology in Pediatrics (6, 1938)
- Henry, James P, M A, M Sc, M R C S C R C P Aero Medical Laboratory, Wright Field, Dayton, Ohio On leave of absence from the University of Southern California, Los Angeles, Calif (1, 1947)
- Henschel, Austin F, Ph D University of Minnesota, Minneapolis Assistant Professor of Physiological Hygiene (1, 1944)
- Hepburn, Joseph Samuel, A M, M S, Ph D, M D Chem D 235 N 15th St, Philadelphia 2, Pa Professor of Chemistry and Research Associate in Gastro-Enterology, Registrar, Hahnemann Medical College and Hospital (2, 1915)
- Hepler, Opal E, Ph D, M D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill Assistant Professor of Pathology (4, 1939)
- Herbst, R M, Ph D Kirtzie Chemical Laboratory, Michigan State College, East Lansing Associate Professor of Chemistry (2, 1938)
- Herrick, C Judson, Ph D 236 Morningside Drive, Grand Rapids, Mich Professor Emeritus of Neurology, University of Chicago, Member of the National Academy of Sciences (1, 1907)
- Herrick, Julia F, M A, Ph D Mayo Foundation, Rochester, Minn Associate Professor of Experimental Medicine (1, 1933)
- Herrin, Raymond C, Ph D, M D University of Wisconsin Medical School, Madison Associate Professor of Physiology (1, 1932)
- Herrington, Lovie P, M A, Ph D 290 Congress Ave, New Haven, Conn Associate Director, John B Pierce Laboratory of Hygiene, Research Associate Professor, Dept of Public Health, Yale Medical School (1, 1942)
- Herrriott, Roger M, Ph D Rockefeller Institute for Medical Research, Princeton, N J Associate (2, 1910)
- Herrmann, George, Ph D, M D University of Texas, Medical Branch, Galveston Professor of Medicine (4, 1925)
- Herrmann, Julian B, Ph B, M D 2 East 94th St, New York 28, N Y (3, 1941)
- Herrmann, Louis George, M D Cincinnati General Hospital, Cincinnati 29, O Associate Professor of Surgery, University of Cincinnati College of Medicine, Attending Surgeon, Surgical Services, Cincinnati General Hospital and Children's Hospital and Christian R Holmes Hospital of University of Cincinnati (4, 1933)
- Hershey, A D, Ph D Washington University School of Medicine, St Louis, Mo Associate Professor of Bacteriology and Immunology (6, 1942)
- Hertig, Arthur T, M D Harvard University Medical School, 221 Longwood Ave, Boston, Mass Assistant Professor of Pathology and Assistant Professor of Obstetrics (4, 1941)
- Hertz, Roy, Ph D, M D National Institute of Health, Bethesda 14, Md P H Surgeon (R), Division of Physiology (1, 1945)
- Hertz, Saul, M D 330 Brookline Ave, Boston, Mass Beth Israel Hospital Instructor, Harvard Medical School (4, 1935)
- Hertzman, Alrick B, Ph D St Louis University School of Medicine, St Louis, Mo Professor of Physiology and Director of the Department (1, 1925)
- Herwick, Robert P, Ph D, M D, LL B U S

- Food and Drug Administration, Washington, D C *Chief, Drug Division, Associate Prof Pharmacology, Georgetown Medical School, Adjunct Clinical Professor Medicine (Therapeutics) George Washington Medical School* (3, 1938)
- Hess, Charles L, M S, M D 308 Davidson Bldg, Bay City, Mich (1, 1916)
- Hess, Walter C, Ph D Georgetown Medical School, 39th St and Reservoir Rd, N W, Washington, D C *Professor of Biological Chemistry* (2, 1935)
- Hetherington, Albert W, M S, Ph D School of Aviation Medicine, Randolph Field, Texas (1, 1943)
- Hewetson, Jean Hawks, M D Biglerville, Pa (5, 1944)
- Hewitt, Earl Albon, M S, Ph D Iowa State College, Ames *Associate Professor of Veterinary Physiology* (1, 1932)
- Hewitt, Julia A W, B A 2631 Central Ave, N E, Minneapolis 13, Minn (6, 1921)
- Heyroth, Francis F, M D, Ph D Kettering Laboratory, College of Medicine, University of Cincinnati, Cincinnati, O *Assistant Professor of Applied Physiology* (2, 1935)
- Hiatt, Edwin P, M A, Ph D North Carolina University School of Medicine, Chapel Hill *Associate Professor of Physiology* (1, 1942)
- Hickman, Kenneth C D, Ph D Distillation Products, Inc, 755 Ridge Road W, Rochester, N Y *Vice-President and Director of Research* (2, 1944)
- Hiestand, William A, Ph D Department of Biology, Purdue University, Lafayette, Ind *Professor of Physiology* (1, 1917)
- Higgins, Harold Leonard, M D 322 Franklin, Newton, Mass (1, 1914, 5, 1933)
- Highman, Benjamin, M D National Institute of Health, Bethesda 14, Md *Senior Assistant, Surgeon (R) Pathology Laboratory* (4, 1947)
- Hill, Edgar S, M S, Ph D Washington University, College of Dentistry St Louis, Mo *Associate Professor of Biological Chemistry and Physiology* (2, 1936)
- Hill, Robert M, M S, Ph D 4200 E 9th Ave, Denver, Colo *Associate Professor of Biochemistry, University of Colorado Medical School* (2, 1933)
- Hill, Samuel E M A, Ph D 18 Collins Ave, Troy, N Y *Research Worker, The Behr Manning Corp* (1, 1934)
- Hiller, Alma, Ph D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Associate* (2, 1929)
- Humwich, Harold E, M D Fallston, Md *Chief, Clinical Research Branch, Medical Division, Army Chemical Center, Maryland* (1, 1925, 5, 1933)
- Humwich, William A, M S, Ph D Toxicology Section, Medical Division, Army Chemical Center, Md (1, 1917)
- Hine, Charles H, M A, Ph D, M D Pharmacology and Toxicology Department, Medical Center, The University of California Medical School, San Francisco 22, Calif *Lecturer in Toxicology, University of California Medical School, Consulting Pharmacologist and Toxicologist, Shell Development Co* (3, 1917)
- Hines, Harry M, M S, Ph D The State University of Iowa, Iowa City *Professor of Physiology* (1, 1928)
- Hines, Marion, Ph D Department of Anatomy, Emory University, Ga *Professor of Experimental Anatomy* (1, 1932)
- Hinrichs, Marie, Ph D, M D Southern Illinois Normal University, Carbondale *Professor of Physiology, Director of Student Health Service* (1, 1928)
- Hinsey, Joseph C, M S, Ph D Cornell University Medical College, 1300 York Ave, New York City *Professor of Anatomy and Dean of the Medical College* (1, 1929)
- Hirschmann, Hans, M D, Ph D Lakeside Hospital, Cleveland, Ohio *Assistant Professor of Biochemistry, Department of Medicine, Western Reserve University* (2, 1946)
- Hisaw, Frederick L, A M, Ph D The Biological Laboratories, Harvard University, Cambridge Mass *Professor of Zoology* (1, 1932)
- Hitchcock, David I, Ph D 333 Cedar St, New Haven, Conn *Associate Professor of Physiology, Yale University* (2, 1930)
- Hitchcock, Fred A, M Sc, Ph D Ohio State University, Columbus *Professor of Physiology* (1, 1927, 5, 1933)
- Hitchcock, Philip, A B, M S, Ph D Department of Physiology and Pharmacology, Medical College of Alabama, Birmingham 5, Ala *Assistant Professor of Physiology and Pharmacology* (3, 1946)
- Hitchings, George H, M S, Ph D 50 Primrose Ave, Tuckahoe 7, N Y *Biochemist, Wellcome Research Laboratories* (2, 1942)
- Hjort, Axel M, M D, Ph D P O Box 281, 14 Fern Way, Scarsdale, N Y *Adjunct Physician, Grasslands Hospital, Valhalla, N Y* (2, 1925)
- Hoagland, Hudson, M S, Ph D, Sc D (hon) 222 Maple Ave, Shrewsbury, Mass *Executive Director, Worcester Foundation for Experimental Biology, Neurophysiologist, Worcester State Hospital, and Research Professor of Physiology, Tufts College Medical School* (1, 1932)
- Hobby, Gladys L, A B, M A, Ph D 11 Bartlett St, Brooklyn 6, N Y *Bacteriologist, Chas Pfizer & Co* (6, 1946)
- Hober, Rudolf University of Pennsylvania Medical School, Philadelphia *Visiting Professor of Physiology* (1, 1936)

- Hodes, Robert, Ph D Johnson Foundation, University of Pennsylvania, Philadelphia *Associate in Biophysics* (1, 1941)
- Hodge, Harold C, Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Professor of Pharmacology and Toxicology* (2, 1937)
- Hoefer, Paul F A, Ph D, M D Neurological Institute of New York, 710 W 168th St, New York 32, N Y *Associate Professor of Neurology* (1, 1945)
- Hoff, Ebbe Curtis, M A, Ph D Medical College of Virginia, Richmond 19 *Associate Professor* (1, 1933)
- Hoff, Hebbel E, M A, Ph D McGill University, Montreal, Quebec, Canada *Professor of Physiology* (1, 1933)
- Hoffman, William Samuel, Ph D, M D 623 S Wood St, Chicago, Ill *Acting Director of Laboratories and Acting Director of the Hektoen Institute for Medical Research, Cook County Hospital* (2, 1935)
- Hofmann, Klaus, Ph D Department of Chemistry, University of Pittsburgh, Pittsburgh, Penn *Research Professor* (2, 1947)
- Hogan, Albert G, A M, Ph D 105 Schweitzer Hall, Columbia, Mo *Professor of Animal Nutrition, University of Missouri* (2, 1916, 5, 1933)
- Hogness, Thorfin R, Ch E, Ph D Department of Chemistry, University of Chicago, Chicago, Ill *Professor of Chemistry* (2, 1941)
- Holck, Harald G O, Ph D College of Pharmacy, University of Nebraska, Lincoln *Associate Professor of Pharmacology* (1, 1935, 3, 1938)
- Hollaender, Alexander, M A, Ph D National Institute of Health, Bethesda 14, Md *Head Biophysicist, Director of Biology Division, Clinton Laboratories* (1, 1947)
- Hollander, Franklin, Ph D Mount Sinai Hospital, Fifth Ave and 100th St, New York City *Associate in Physiology, Head, Gastro-Enterology Research Laboratory* (1, 1942, 2, 1932)
- Holm, August, Sc D E R Squibb & Sons, New Brunswick, N J *Head, Bacteriology Developing Laboratories* (6, 1946)
- Holman, Russell Lowell, M D Louisiana State University School of Medicine, New Orleans, La *Professor of Pathology* (4, 1940)
- Holmes, Arthur Dunham, Ph D University of Massachusetts, Amherst *Research Professor of Chemistry* (2, 1931, 5, 1933)
- Holmes, Joseph H, M D, D Med Sc University of Colorado School of Medicine, 4200 E Ninth Ave, Denver 7 *Assistant Professor of Physiology* (1, 1947)
- Holmes, Julia O, M S, Ph D University of Massachusetts, Amherst *Research Professor of Nutrition* (2, 1942, 5, 1936)
- Holt, Joseph Paynter, M S, M D, Ph D Standard Oil Co, Room 2400, 30 Rockefeller Plaza, New York 20, N Y *Director of Medical Research* (1, 1942)
- Holt, L Emmett, Jr, M D 477 First Ave, New York 16, N Y *Professor of Pediatrics, New York University College of Medicine* (2, 1930, 5, 1946)
- Hoobler, Icie Macy, M S, Ph D, Sc D 660 Frederick St, Detroit, Mich *Director, Research Laboratory Children's Fund of Michigan* (2, 1925, 5, 1933)
- Hooker, Davenport, M A, Ph D University of Pittsburgh School of Medicine, Pittsburgh, Pa *Professor of Anatomy* (1, 1920)
- Hooker, Sanford B, A M, M D 80 E Concord St, Boston, Mass *Member, Evans Memorial* (6, 1918)
- Hoover, Sam R, M A, Ph D 7815 Linden Rd, Philadelphia 18, Pa *Senior Chemist Eastern Regional Research Laboratory, U S Department of Agriculture* (2, 1946)
- Hoppert, C A, Ph D Michigan State College, Box 626, East Lansing *Professor of Biological Chemistry* (5, 1935)
- Hopps, Howard C, M D Department of Pathology, University of Oklahoma School of Medicine, 801 E 13th St, Oklahoma City, Okla *Professor of Pathology and Chairman of Dept* (4, 1947, 6, 1946)
- Horecker, Bernard L, Ph D National Institute of Health, Bethesda 14, Md *Biochemist* (2, 1947)
- Horowitz, Norman H, Ph D California Institute of Technology, Pasadena, Calif *Associate Professor of Biology* (2, 1946)
- Horsfall, Frank L, Jr, M D, C M Rockefeller Institute, 66th St and York Ave, New York City *Member* (6, 1937)
- Horvath, Steven M, M A, Ph D Dept of Physical Medicine, Hospital of the Univ of Pennsylvania, Philadelphia, Pa (1, 1943)
- Horwitt, M K, Ph D Biochemical Research Laboratory, Elgin State Hospital, Elgin, Ill *Director, Biochemical Research Laboratory, Assistant Professor, Physiological Chemistry, University of Illinois School of Medicine* (2, 1941)
- Hoskins, R G, Ph D, M D Harvard Medical School, Boston, Mass *Research Associate in Physiology, Harvard University, Director of Research, Memorial Foundation for Neuroendocrine Research* (1, 1911)
- Hotchkiss, Rollin D, Ph D The Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Associate* (2, 1941)
- Houck, C Riley, A M, Ph D University of Tennessee Medical School, Memphis 3 *Assistant Professor in Physiology* (1, 1947)

- Hove, Edwin L, M S, Ph D Distillation Products, Inc, 755 Ridge Road, West, Rochester 13, N Y *Research Biochemist* (5, 1946)
- Howard, Evelyn, A M, Ph D Johns Hopkins School of Medicine, Baltimore, Md *Instructor in Physiology* (1, 1933)
- Howard, John Eager, A B, M D Johns Hopkins Hospital, Baltimore 5, Md *Assistant Professor of Medicine* (1, 1946)
- Howard, Marion E, M D New Haven Hospital, New Haven, Conn *Associate Clinical Professor of Medicine, Yale School of Medicine, Associate Physician, New Haven Hospital and New Haven Dispensary* (1, 1939, 6, 1937)
- Howe, Paul E, A M, Ph D Bureau of Animal Industry, U S Dept of Agriculture, Washington 25, D C *Chief, Animal Nutrition Division, and Assistant Chief, Bureau of Animal Industry* (1, 1913, 2, 1909, 5, 1933)
- Howe, Percy R, M D, D D S Harvard Medical School, Boston, Mass *Director Forsyth Dental Infirmary, Professor Dental Sciences, Instructor in Pathology* (5, 1935)
- Howell, Katherine M, M D 6830 S Merrill Ave, Chicago, Ill *Head of Departments of Bacteriology and Serology* (6, 1940)
- Howell, Stacey F, Ph D V D Research Laboratory, U S Marine Hospital, Stapleton, Staten Island, N Y *Chemist, U S Public Health Service* (2, 1940)
- Hubbard, Roger Sanford, A M, Ph D 546 Delaware Ave, Buffalo 2, N Y *Biochemist, Buffalo General Hospital, Professor of Applied Physiology, Buffalo University Medical School* (1, 1922, 2, 1920)
- Hubbell, Rebecca B, M S, Ph D Connecticut Agricultural Experiment Station, New Haven *Assistant Biochemist* (2, 1937, 5, 1935)
- Hudaek, Stephen Sylvester, M D 180 Fort Washington Ave, New York, N Y *Associate Professor of Orthopedic Surgery, Columbia Univ* (4, 1933)
- Huddleston, Ora Leonard, M D, Ph D Los Angeles County General Hospital, 1900 N State St, Los Angeles 33, Calif (1, 1936)
- Hueper, Wilhelm C, M D Warner Institute for Therapeutic Research, 113 W 18th St, New York City 11 *Pathologist* (4, 1940)
- Huffman, C F, M S, Ph D Michigan State College, East Lansing *Research Professor and Professor in Dairy Husbandry* (5, 1937)
- Huffman, Max N, B A, Ph D Southwestern Medical College, 2211 Oak Lawn, Dallas, Texas *Research Professor of Biochemistry* (2, 1947)
- Huggins, Charles Brenton, M D University of Chicago, Chicago, Ill *Professor of Surgery* (1, 1932)
- Hughes, Hettie B, M S, Ph D The Christ Hos-
- pital, Cincinnati 19, Ohio *Research Associate* (2, 1916)
- Hughes, Joseph, M D 111 N 49th St, Philadelphia, Pa *Assistant Professor of Experimental Neurology, Graduate School of Medicine, University of Pennsylvania, Director of Laboratory, Pennsylvania Hospital for Mental Diseases* (1, 1936)
- Hughes, Josiah Simpson, M A, M S, Ph D Kansas State College, Manhattan *Professor of Chemistry* (2, 1931, 5, 1939)
- Hughes, Thomas P, A M, Ph D Caixa Postal 49, Rio de Janeiro, Brazil *Member of Staff, International Health Division* (6, 1934)
- Hulpieu, Harold R, M A, Ph D Indiana University School of Medicine, Indianapolis *Associate Professor of Pharmacology* (3, 1939)
- Hunscher, Helen A, Ph D Western Reserve University, 2023 Adelbert Rd, Cleveland 6, O *Head of Department of Home Economics* (5, 1931)
- Hunt, Reid, M D, Ph D, Sc D Harvard Medical School, Boston, Mass *Professor Emeritus of Pharmacology, Harvard University, Member, National Academy of Sciences* (1, 1895, 2, 1906, 3, 1908)
- Hunter, Andrew, M A, M B, F R S C University of Toronto, Toronto, Canada *Professor of Pathological Chemistry* (2, 1908)
- Hunter, Francis Edmund, Jr, Ph D Pharmacology Department, Washington University Medical School, St Louis 10, Mo *Assistant Professor of Pharmacology* (2, 1946)
- Hunter, George, M A, D Sc, F R S C University of Alberta, Edmonton, Canada *Professor of Biochemistry* (2, 1924)
- Hunter, Jesse E, M S, Ph D Allied Mills, Inc, 7500 S Adams St, Peoria, Ill *Director of Research* (5, 1936)
- Hussey, Raymond, M D Medical Science Center of Wayne University, 1547 Penobscot Building, Detroit 26, Mich *Director, Institute for Occupational Health Research, Dean and Professor of Occupational Health, School of Occupational Health* (4, 1927)
- Hutchens, John O, Ph D Department of Physiology, University of Chicago, Chicago 37, Ill *Associate Professor of Physiology and Chairman of the Department, Director of the Toxicity Laboratory* (1, 1947)
- Ingalls, Mabel S, Ph D Salisbury Mills, Orange County, N Y (6, 1940)
- Ingle, Dwight J, M S, Ph D The Upjohn Co, Research Department, Kalamazoo, Mich *Upjohn Research Fellow* (1, 1939)
- Ingraham, Raymond Clifford, Ph D College of Medicine, University of Illinois, 1853 W Polk St, Chicago *Assistant Professor in Physiology* (1, 1938)

- Ingram, W R, Ph<sup>D</sup> College of Medicine, The State University of Iowa, Iowa City *Professor and Head of the Department of Anatomy* (1, 1936)
- Irvin, J Logan, Ph D Johns Hopkins University School of Medicine, 710 N Washington St, Baltimore, Md *Assistant Professor of Physiological Chemistry* (2, 1942)
- Irving, George Washington, Jr, M A, Ph D Agricultural Research Center, Beltsville, Md *Biochemist, Head, Division of Biologically Active Compounds, U S Department of Agriculture* (2, 1946)
- Irving, Laurence, A M, Ph D Swarthmore College, Swarthmore, Pa *Lt Col, A C Professor of Experimental Biology* (1, 1927)
- Irwin, M R, Ph D Department of Genetics, University of Wisconsin, Madison *Professor of Genetics* (6, 1936)
- Isaacs, Raphael, M D 104 S Michigan Ave, Suite 630, Chicago 3, Ill *Attending Physician, Department of Hematology, Michael Reese Hospital* (4, 1928)
- Isenberger, R M, M A, M D University of Kansas School of Medicine, Kansas City *Professor of Pharmacology* (3, 1937)
- Ivy, Andrew C, Ph D, M D, D Sc 1853 West Polk St, Chicago 12, Ill *Vice-President and Distinguished Professor of Physiology, University of Illinois* (1, 1919, 5, 1933)
- Izquierdo, J Joaquin, M D National School of Medicine, Mexico City *Professor of Physiology in the National School of Medicine and the Escuela Medico Militar de Mexico* (1, 1928)
- Jackson, Dennis Emerson, A M, Ph D M D University of Cincinnati Medical School, Eden and Bethesda Aves, Cincinnati, O *Professor of Pharmacology* (1, 1910, 3, 1912)
- Jackson, Eugene L, Ph D 12 S 12th St, Richmond 19, Va *Medical Director, A H Robins Co* (3, 1942)
- Jackson, Richard W, Ph D Northern Regional Research Laboratory, U S Department of Agriculture, 825 N University St, Peoria 5, Ill *Head of Fermentation Division* (2, 1930, 5, 1933)
- Jacobs, Merkel Henry, Ph D University of Pennsylvania, Philadelphia *Professor of General Physiology, Member of the National Academy of Sciences* (1, 1919)
- Jacobs, Walter A, A M, Ph D Rockefeller Institute, 66th St and York Ave, New York City *Member, Member, National Academy of Sciences* (2, 1908, 3, 1913)
- Jacobson, Edmund, Ph D, M D Laboratory for Clinical Physiology, 55 E Washington St, Chicago, Ill (1, 1929)
- Jaffe, Henry L, M D Hospital for Joint Diseases, 1919 Madison Ave, New York City *Director of Laboratories* (4, 1925)
- Jahn, Theodore Louis, Ph D State University of Iowa, Iowa City *Associate Professor of Zoology* (1, 1944)
- Jamieson, Walter A, Sc D (hon) Eli Lilly & Company, Indianapolis, Ind *Director, Biological Division* (6, 1927)
- Jandorf, Bernard J, M, Ph D, Medical Division, Army Chemical Center, Md *Research Biochemist, Biochemistry Section, Lecturer in Preventive Medicine, Johns Hopkins University School of Medicine* (2, 1916)
- Jansen, Eugene F, B A Enzyme Research Laboratory, Western Regional Research Laboratory, Albany 6, Calif *Senior Chemist, Bureau of Agricultural and Industrial Chemistry, U S Department of Agriculture* (2, 1917)
- Jacques, L B, M A, Ph D Univ of Saskatchewan, Saskatoon, Sask, Canada *Professor of Physiology* (1, 1913)
- Jasper, Herbert H, M A, Ph D, D Sc St. Montreal Neurological Institute, 3801 University St, Montreal, Que, Canada *Lecturer in Neuroelectrography and Director of Department of Electrophysiology* (1, 1940)
- Jean, P C, M D State University of Iowa, Iowa City *Professor of Pediatrics* (5, 1937)
- Jensen, H, Ph D Medical Dept Field Research Laboratory, Fort Knox, Kentucky *Chief Biochemist* (2, 1929)
- Jobling, James W, M D Columbia University, 630 W 168th St, New York City *Professor of Pathology* (1, 1913)
- Jochim, Kenneth E, Ph D St Louis School of Medicine, 1102 S Grand Blvd, St Louis 1 (1, 1912)
- Johlin, J M, Ph D D Sc Vanderbilt University School of Medicine, Nashville Tenn *Associate Professor of Biochemistry* (2, 1928)
- Johnson, B Connor, M A, Ph D, Division of Animal Nutrition, University of Illinois, Urbana, Ill *Assistant Professor* (2, 5, 1917)
- Johnson, Frank H, A M, Ph D Princeton University, Princeton, N J *Assistant Professor, Dept of Biology* (1, 1942)
- Johnson, Joseph L, Ph D, M D School of Medicine, Howard University, Washington, D C *Professor and Head of the Department of Physiology* (1, 1934)
- Johnson, J Raymond, Ph D Long Island College of Medicine, 350 Henry St, Brooklyn, N Y *Associate Professor and Acting Director of Department of Physiology and Pharmacology* (1, 1938)
- Johnson, Marvin J, M S, Ph D University of Wisconsin, Madison *Professor of Biochemistry* (2, 1941)
- Johnson, Robert E, M D, Ph D Army Medical

- Nutrition Laboratory, 1819 W Pershing Rd, Chicago 9, Ill *Director* (1, 1911, 2, 1939, 3, 1916)
- Johnson, S R, M S, Ph D Animal Industry Department, University of Arkansas Fayetteville, Ark *Associate Professor* (5, 1947)
- Johnson, Victor, Ph D, M D Vivo Foundation, Rochester, Minn (1, 1933)
- Johnston, Charles G, M S, M D Wayne University College of Medicine, Detroit, Mich *Professor of Surgery* (1, 1933)
- Johnston, Margaret W, Ph D B 152, University Hospital, Ann Arbor, Mich *Research Associate in Internal Medicine* (2, 1930, 5, 1938)
- Jolliffe, Norman, M D 39 E 75th St, New York, N Y (1, 1932)
- Jones, D Breese, Ph D Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U S Department of Agriculture, Beltsville, Md *Protein Chemist* (2, 1920, 5, 1935)
- Jones, James H, M S, Ph D School of Veterinary Medicine, University of Pennsylvania, Philadelphia *Professor of Physiological Chemistry* (2, 1928, 5, 1933)
- Jones, Kenneth K, M S, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Associate Professor of Physiology and Pharmacology* (1, 1936)
- Jones, Lloyd R, M S, Ph D 1402 S Grand Blvd, St Louis, Mo *Professor and Chairman of Department of Bacteriology, St Louis University School of Medicine* (6, 1933)
- Joseph, Norman R, Ph D University of Illinois, 1853 West Polk Street, Chicago 12, Ill *Assistant Professor of Chemistry* (2, 1947)
- Joslin, Elliott P, M A, M D New England Deaconess Hospital, 81 Bay State Rd, Boston, Mass *Director, George F Baker Clinic* (5, 1933)
- Jukes, Thomas Hughes, Ph D Lederle Laboratories, Pearl River, N Y *Head, Department of Nutrition and Physiology Research* (2, 1935, 5, 1938)
- Jung, Frederic Theodore, Ph D, M D Northwestern University Medical School, Chicago, Ill *Assistant Professor of Physiology and Pharmacology* (1, 1930)
- Jungeblut, Claus W, M D College of Physicians and Surgeons, 630 W 168th St, New York City *Professor of Bacteriology, Columbia University* (4, 1929, 6, 1926)
- Kabat, Elvin A, A M, Ph D The Neurological Institute, 710 W 168th St, New York 32, N Y *Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University and The Neurological Institute* (2, 1940, 6, 1943)
- Kabat, Herman, Ph D M D 2633 16th St, N W, Washington, D C *Consultant in Neurology, Health Department, District of Columbia* (1, 1911)
- Kahn, Reuben L, Sc D, LL D University of Michigan Hospital, Ann Arbor *Director of Clinical Laboratories* (4, 1931, 6, 1919)
- Kalekar, Herman M, M D, Ph D Institute for Medical Physiology, University of Copenhagen, 28 Juliane Varies Vej Copenhagen, Denmark *Associate Professor* (2, 1912)
- Kamen, Martin D, Ph D Washington University Medical School, 510 S Kingshighway, St Louis 10, Mo *Associate Professor of Chemistry* (2, 1946)
- Kamm, Oliver, M S, Ph D Research Laboratory, Parke, Davis & Co, Detroit, Mich *Scientific Director* (2, 1928)
- Karel, Leonard, Ph D Research Grants Division, National Institute of Health, Building 1, Bethesda 14, Md (3, 1947)
- Karpovich, Peter V, M D, M P C Springfield College, Springfield, Mass *Professor of Physiology* (1, 1942)
- Karshan, Maxwell, Ph D Department of Biological Chemistry, Columbia University, 630 W 168th St, New York City *Associate Professor of Biochemistry* (2, 1939)
- Karsner, Howard T, M D Western Reserve University, 2085 Adelbert Rd, Cleveland, O *Professor of Pathology, Director of the Institute of Pathology* (4, 1913, 6, 1925)
- Katz, Louis Nelson, A M, M D 2900 Ellis Ave, Chicago, Ill *Director of Cardiovascular Research, Michael Reese Hospital, Professorial Lecturer in Physiology, University of Chicago* (1, 1924)
- Katzman, Philip A, Ph D St Louis University School of Medicine, 1402 S Grand Blvd, St Louis 4, Mo *Associate Professor of Biochemistry* (2, 1935)
- Kaulbersz, Jerzy, Ph D, M D Collegium Medica, Grzegorzeczka 16, Cracow, Poland *Professor of Physiology* (1, 1944)
- Kaunitz, Hans, M D College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, N Y *Research Associate in Pathology* (4, 1947)
- Kay, H D, Ph D, D Sc, F R S National Institute for Research in Dairying, Shinfield, near Reading, England *Director, Research Professor of Biochemistry, University of Reading* (2, 1930)
- Kazal, Louis A, Ph D Medical Research Division, Sharp & Dohme, Inc, Glenolden, Penn *Research Biochemist* (2, 1947)
- Keeton, Robert W, M S, M D University of Illinois College of Medicine, 1853 W Polk St, Chicago *Professor of Medicine* (1, 1916, 3, 1924)
- Kehoe, Robert A, M D Kettering Laboratory

- of Applied Physiology, College of Medicine, University of Cincinnati, Eden Ave, Cincinnati, O *Research Professor of Physiology* (1, 1940)
- Keith, Norman M, M D Mayo Clinic, Rochester, Minn *Consulting Physician, Division of Medicine, Mayo Clinic, Professor of Medicine, Mayo Foundation, University of Minnesota* (1, 1920, 3, 1932, 4, 1924)
- Keith, T B, Ph D Animal Industry and Range Management, Agricultural Experiment Station, Bozeman, Mont *Associate Professor* (5, 1911)
- Kellaway, Peter E, M A, Ph D Department of Physiology, McGill University, Montreal, P Q, Canada *Assistant Professor* (1, 1917)
- Keller, Allen D, Ph D Baylor College of Medicine, Houston, Texas *Professor of Physiology, Chairman of Department of Physiology and Pharmacology* (1, 1931)
- Kelser, Raymond A, D V M, Ph D 130 Valley Rd, Ardmore, Pa *Professor of Bacteriology and Dean of Faculty School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pa* (4, 1932)
- Kelsey, F Ellis, B S, Ph D University of Chicago, Chicago, Ill *Research Associate (Instructor) in Pharmacology* (3, 1941)
- Kelsey, Frances Kathleen O, M S, Ph D University of Chicago, Chicago, Ill *Research Assistant in Pharmacology* (3, 1941)
- Kemmerer, A R, Ph D University of Arizona, Tucson, Arizona *Head, Dept of Human Nutrition* (5, 1946)
- Kempner, Walter, M D Duke University School of Medicine, Durham, N C *Assistant Professor of Medicine* (1, 1940)
- Kendall, Edward C, M S, Ph D, D Sc 627 Eighth Ave, S W, Rochester, Minn *Professor of Biochemistry, Mayo Foundation, University of Minnesota* (1, 1916, 2, 1913, 4, prior to 1920)
- Kendall, Forrest E, Ph D 240-06-53rd Ave Douglaston, Long Island, N Y *Assistant Professor of Biochemistry, Research Service, Columbia Division, Goldwater Memorial Hospital, Welfare Island, N Y* (6, 1943)
- Kennard, Margaret A, M D Psychiatric Division, Bellevue Hospital, First Ave & 30th St, New York City (1, 1934)
- Kennedy, Cornelia, M A, Ph D Snyder Hall, University Farm, St Paul, Minn *Associate Professor of Agricultural Biochemistry, University of Minnesota, Assistant Chemist, Minnesota Experiment Station* (2, 1924, 5, 1934)
- Kennedy, Robert P, M D Knollwood Drive, R D 1, Rochester, N Y (4, 1929)
- Kent, John F, M A Army Medical Center, Washington 12, D C *Chief, Research Section, Department of Serology, Army Medical Department Research and Graduate School* (6, 1947)
- Kenton, Harold B, Ph D New England Deaconess Hospital, Boston, Mass *Bacteriologist and Director of the Blood Bank* (6, 1934)
- Kenyon, Allan T, M D University of Chicago, Division of Biological Sciences, 950 E 59th St, Chicago, Ill *Assistant Professor of Medicine* (3, 1910)
- Keresztesy, John C, M A, Ph D National Institute of Health, Bethesda 14, Md *Scientist Officer, Division of Physiology* (2, 1911, 5, 1915)
- Kerr, Stanley E, Ph D American University of Beirut, Beirut, Lebanon, Syria *Professor of Biological Chemistry* (2, 1937)
- Kerr, Wm J, M D University of California Hospital, Third and Parnassus Aves, San Francisco *Professor of Medicine, University of California, Physician-in-Chief, University of California Hospital* (3, 1930)
- Kesten, Homer D, M D College of Physicians and Surgeons, Columbia University, New York City *Associate Professor of Pathology* (4, 1931)
- Kety, Seymour S, M D Dept of Pharmacology, Medical School, University of Pennsylvania, Philadelphia 1 *Associate in Pharmacology, Medical School, Assistant Visiting Physician in Medicine, Philadelphia General Hospital* (3, 1915)
- Keys, Ancel, M A, Ph D, D Phil Stadium South Tower, University of Minnesota, Minneapolis *Professor and Director of Laboratory of Physiological Hygiene* (1, 1939, 2, 1936)
- Kidd, John G, M D Cornell University Medical College, 1300 York Ave, New York City *Professor of Pathology, Pathologist, New York Hospital* (4, 1938, 6, 1937)
- Kik, M C, Ph D College of Agriculture, University of Arkansas, Fayetteville *Associate Professor of Agricultural Chemistry* (5, 1942)
- Kilborn, Leslie G, M A, M D, Ph D 47 Warren Road, Toronto, Ontario, Canada At present West China Union University, Chengtu, Sze, China (1, 1928)
- Killian, John Allen, A M, Ph D Killian Research Laboratories, Inc, 49 W 45th St, New York City (2, 1921)
- Kinard, F W, M S, Ph D, M D Medical College of the State of South Carolina, Charleston 16 *Associate Professor of Physiology* (1, 1917)
- King, Barry G, M A, Ph D Medical Service, Safety Regulations, Civil Aeronautics Administration, Department of Commerce, Washington, D C *Chief, Aeromedical Design and Material Division* (1, 1938)
- King, Charles Edwin, Ph D Vanderbilt University, Nashville, Tenn *Associate Professor of Physiology* (1, 1916)
- King, Charles Glen, Ph D Nutrition Founda-



- tion, Inc , Chrysler Building, New York City  
*Scientific Director, Professor of Chemistry, Columbia University* (2, 1931, 5, 1933)
- King, Jessie Luella, Ph D Goucher College, Baltimore, Md *Professor of Physiology* (1, 1911)
- King, Joseph T, M D , Ph D 314 Millard Hall, University of Minnesota Medical School, Minneapolis *Associate Professor of Physiology* (1, 1931)
- King, Lester S , M D Illinois Masonic Hospital, Chicago, Ill *Director of Laboratories, Clinical Assistant Professor of Pathology, University of Illinois* (1, 1911)
- Kirchhof, Anton C, M S , M D Division of Anesthesiology, University of Oregon Medical School, Portland 1, Ore *Research Associate, Department of Pharmacology* (3, 1917)
- Kirk, Paul L , Ph D University of California, Berkeley *Professor of Biochemistry* (2, 1933)
- Kirkbride, Mary B, Sc D 311 State St , Albany 6, N Y (6, 1921)
- Kisch, Bruno, M D 845 West End Ave , New York City *Professor of Biochemistry, Yeshiva University* (1, 1943)
- Kleiber, M, D Sc University of California, Davis *Professor of Animal Husbandry* (1, 1943, 5, 1933)
- Klein, J Raymond, Ph D University of Illinois, Neuropsychiatric Institute, 912 S Wood St , Chicago *Biochemist and Assistant Professor of Psychiatry and Physiological Chemistry* (2, 1941)
- Kleiner, Israel Simon, Ph D New York Medical College, Flower and Fifth Avenue Hospitals, New York 29, N Y *Professor of Physiology and Biochemistry* (1, 1911, 2, 1912, 3, 1912, 5, 1933)
- Kleitman, Nathaniel, A M , Ph D University of Chicago, Chicago, Ill *Associate Professor of Physiology* (1, 1923)
- Klemperer, Friedrich Wilhelm, M D Trudeau Foundation, Trudeau, N Y *Head of Department of Biochemistry* (2, 1941)
- Kletzien, Seymour W, M S , Ph D , 330 S Ninth St , Philadelphia, Pa *Nutrition Research Clinic, Philadelphia Living In & Pennsylvania Hospitals Biochemist* (5, 1933)
- Kline, O L , Ph D Federal Security Agency, Food and Drug Administration, Washington, D C *Biochemist* (5, 1936)
- Kline, Raymond F, B S , M S Physiological Lab Univ of Virginia Med School, Charlottesville, Va *Instructor in Physiology* (1, 1946)
- Klotz, Irving M, Ph D Department of Chemistry, Northwestern University, Evanston, Ill *Assistant Professor of Chemistry* (2, 1947)
- Klüver, Heinrich, Ph D University of Chicago, Chicago, Ill *Professor of Experimental Psychology* (1, 1935)
- Knight, C Arthur, Ph D The Rockefeller Inst for Med Research, Princeton, N J *Associate* (2, 1946)
- Knoefel, Peter K, M A , M D University of Louisville, 101 W Chestnut St , Louisville, Ky *Professor of Pharmacology* (3, 1934)
- Knowlton, Frank P, A M , M D 1356 Westmoreland Ave , Syracuse, N Y *Syracuse University College of Medicine, Syracuse, N Y Emeritus Professor of Physiology* (1, 1911)
- Knowlton, G Clinton, Ph D Room 101, Physiology Bldg , Emory University, Ga (1, 1938)
- Knudson, Arthur, Ph D Albany Medical College, New Scotland Ave , Albany, N Y *Professor of Biochemistry and Associate Dean* (2, 1919, 5, 1936)
- Knutti, Ralph Eddy, M D Children's Hospital, Los Angeles, Calif *Director of Laboratories, Assistant Professor of Pathology, University of Southern California* (4, 1933)
- Kober, Philip A, B S Sherman Laboratories, Detroit, Mich *Director of Research* (2, 1912)
- Koch, Elizabeth M, M A , Ph D 1534 E 59th St , Chicago, Ill (2, 1925)
- Koch, Fred Conrad, M S , Ph D 1534 East 59th St , Chicago, Ill *Director of Biochemical Research, Armour Laboratories, Professor of Biochemistry Emeritus, University of Chicago* (2, 1912, 5, 1933)
- Kochakian, Charles D, A M , Ph D University of Rochester Medical School, 260 Crittenden Blvd , Rochester, N Y *Assistant Professor, Dept of Vital Economics* (1, 1942)
- Kocher, Rudolph Alfred, M D Box 936, Carmel, Calif *Director, Velie Metabolic Clinic* (2, 1915)
- Koehler, Alfred E, M D , Ph D 317 W Pueblo St , Santa Barbara, Calif *Physician, Sansum Clinic, Santa Barbara Cottage Hospital* (2, 1924)
- Koehne, Martha, Ph D 285 15th Ave , Apt 22, Columbus, Ohio *Nutritionist, Ohio State Dept of Health* (5, 1933)
- Koelle, George B, B Sc , Ph D Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md *Chalfont Fellow in Ophthalmology* (3, 1947)
- Koepf, George F, M D 537 Delaware Ave , Buffalo 2, N Y *Associate in Physiology, University of Buffalo* (1, 1942)
- Koerber, Walter L, Ph D E R Squibb & Sons, New Brunswick, N J *Assistant Department Head* (6, 1943)
- Kohlstaedt, Kenneth G, M D Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis 7, Ind *Director* (1, 1947)
- Kohn, Henry I, Ph D Division of Biology, Clinton Laboratories, Oak Ridge, Tenn *Senior Assistant Surgeon, U S Public Health Service* (1, 1940)

- Kolmer, John A, M S, M D, D P H, Sc D, LL D, L H D 1 Montgomery Ave, Bala-Cynwyd, Pa Professor of Medicine, Temple University, Director, Research Institute of Cutaneous Medicine (6, 1913)
- Komarov, Simon A, M S, M D, Ph D S S Fels Fund, Med Research Laboratory, 255 S 17th St, Philadelphia, Pa Director of Dept of Biochemistry (1, 1933)
- Kopeloff, Nicholas, Ph D New York State Psychiatric Institute, 723 W 168th St, New York City Principal Research Bacteriologist, New York State Psychiatric Institute and Hospital (6, 1937)
- Koppányi, Theodore, Ph D Georgetown University, Washington, D C Professor of Pharmacology (1, 1924, 3, 1935)
- Korr, Irwin M, M A, Ph D Kirksville College of Osteopathy & Surgery, Kirksville, Mo Professor of Physiology (1, 1939)
- Kottke, Frederic J, M S, Ph D, M B, M D University of Minnesota, Minneapolis Baruch Fellow in Physical Medicine (1, 1917)
- Kozelka, Frank L, Ph D Dept of Pharmacology and Toxicology, University of Wisconsin, Madison Assistant Professor of Toxicology On leave Captain, Sn C (3, 1939)
- Krahl, Maurice E, Ph D Washington Univ School of Medicine, St Louis 10, Mo Assistant Professor of Pharmacology (2, 1939)
- Krakower, Cecil Alexander, M D University of Illinois College of Medicine, 1853 West Polk St, Chicago Associate Professor of Pathology (1, 1945)
- Kramer, Benjamin, A M, M D 60 Plaza St, Brooklyn, N Y Pediatrician-in-Chief, Brooklyn Jewish Hospital, Professor of Clinical Pediatrics, Long Island College Medical School (1, 1915, 2, 1914)
- Kramer, Martha, Ph D Kansas State College, Manhattan Assistant Dean, School of Home Economics (5, 1933)
- Kramer, S D, M D, Ph D 92 Washington Square, East Salem, Mass Urologist (6, 1944)
- Krampitz, Lester O, Ph D Biochemistry Department, Western Reserve University, Cleveland, Ohio Associate Professor (2, 1946)
- Krantz, John C, Jr, M S, Ph D University of Maryland Medical School, Baltimore Professor of Pharmacology (3, 1937)
- Krauss, William E, Ph D Ohio Agricultural Experiment Station, Wooster Associate Director (2, 1932, 5, 1933)
- Kraybill, Henry R, M S, Ph D 5720 Woodlawn Ave, Chicago 37, Ill Professorial Lecturer, Department of Biochemistry, University of Chicago, Director, Department of Scientific Research, American Meat Institute (2, 1942)
- Krayer, Otto, M D Harvard Medical School, 25 Shattuck St, Boston, Mass Associate Professor of Comparative Pharmacology (3, 1938)
- Krehl, Willard A, Ph D Yale University, 333 Cedar Street, New Haven, Conn Assistant Professor of Nutrition (2, 1917)
- Krop, Stephen, M S, Ph D Medical Division, Army Chemical Center, Md Chief, Pharmacology Section (3, 1911)
- Krueger, Albert Paul, M D University of California, Berkeley Professor of Bacteriology, and Lecturer in Medicine Chairman, Department of Bacteriology, (1, 1930, 6, 1937)
- Krueger, Hugo M, Ph D American Univ of Beirut, Beirut, Lebanon Director of Dept of Pharmacology (1, 1931, 3, 1935)
- Krumbhaar, Edward B, M D, Ph D University of Pennsylvania Medical School, Philadelphia Professor of Pathology (1, 1911, 1, prior to 1920)
- Kruse, Harry Dayton, M D, Sc D Milbank-Memorial Fund, 10 Wall St, New York City (2, 1933)
- Kruse, Theophile K, A M, Ph D University of Pittsburgh Medical School, Pittsburgh, Pa Professor of Physiology and Pharmacology (1, 1919, 3, 1920)
- Kubieck, William G, Ph D Department of Physiology, University of Minnesota, Minneapolis Assistant Professor (1, 1917)
- Kubie, Lawrence S, M D 7 E 81st St, New York City Associate in Neurology, College of Physicians and Surgeons, Columbia University (1, 1928)
- Kuhn, Harry A, M S, Ph B 3915 Fulton St, N W, Washington, D C Colonel, C W S, War Department, Executive Officer, C W Procurement District (3, 1927)
- Kuhn, L Roland, Ph D 6th Army Area Lab Fort Baker, Calif Major, 1 U S Bacteriologist (6, 1939)
- Kuizenga, Marvin H, M Sc, Ph D The Upjohn Company, Kalamazoo, Mich Department Head, Pharmacology-Endocrinology (2, 1947)
- Kunde, Margaret M, Ph D, M D 30 N Michigan Ave, Chicago, Ill Instructor in Medicine, Northwestern University Medical School, Clinical Assistant in Endocrinology, Cook County Hospital (1, 1924)
- Kunitz, Moses, Ph D The Rockefeller Institute for Medical Research, Princeton, N J Associate Member (2, 1947)
- Kurtz, Alton C, Ph D Department of Biochemistry, Medical School, University of Oklahoma, Oklahoma City Associate Professor (2, 1942)
- Kuyper, Adrian C, M S, Ph D Wayne University College of Medicine, Detroit 26, Mich Assistant Professor of Physiological Chemistry (2, 1946)

- Kydd, David M., M.D. Mary Imogene Bissett Hospital, Cooperstown, N. Y. *Associate Physician* (5, 1934)
- Kyes, Preston, A.M., Sc.D., M.D. North Jay, Me. *Professor Emeritus of Preventive Medicine, University of Chicago* (6, 1918)
- Kyker, Granvil C., Ph.D. Department of Biological Chemistry and Nutrition, University of North Carolina School of Medicine, Chapel Hill, N.C. *Associate Professor* (2, 1947)
- Lacey, Robert W., M.S., Ph.D. Department of Physiology and Pharmacology, Southwestern Medical College, Dallas 1, Texas. *Professor of Physiology* (1, 1947)
- Lacy, G. R., M.D. University of Pittsburgh, Pittsburgh, Pa. *Professor of Bacteriology and Immunology* (1, 1927)
- Lalich, Joseph J., M.D. Dept. of Pathology, University of Wisconsin, 426 North Charter St., Madison 6, Wis. *Instructor in Pathology* (1, 1946)
- Lamb, Alvin R., M.S., Ph.D. Experiment Station, Hawaiian Sugar Planters' Association, Honolulu. *Research Associate* (2, 1923, 5, 1934)
- Lambert, Edward H., Ph.D., M.D. Mayo Foundation, Rochester, Minn. *Assistant Professor of Physiology* (1, 1945)
- Lambert, Robert A., M.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Associate Director for the Medical Sciences* (4, 1922)
- Lampen, J. Oliver, Ph.D. Washington University School of Medicine, 4580 Scott Avenue, St. Louis, Mo. *Instructor* (2, 1947)
- Lamport, Harold, M.D. Yale University School of Medicine, New Haven, Conn. *Associate Professor of Physiology* (1, 1943)
- Lamson, Paul Dudley, M.D. Vanderbilt University Medical School, Nashville, Tenn. *Professor of Pharmacology* (1, 1921, 3, 1915)
- Lancefield, Rebecca C., Ph.D. 4 Kenmore Rd., Douglaston, Long Island, N. Y. *Associate Member, Rockefeller Institute for Medical Research* (6, 1933)
- Landis, Carney, Ph.D. Psychiatric Institute and Hospital, Columbia University, 722 W. 168th St., New York City. *Principal Research Psychologist and Professor of Psychology* (1, 1939)
- Landis, Eugene Markley, Ph.D., M.D. Department of Physiology, Harvard Medical School, 25 Shattuck St., Boston, Mass. *George Higginson Professor of Physiology* (1, 1928)
- Landowne, Milton, M.D. Department of Medicine, University of Chicago, Chicago 37, Ill. *Assistant Professor* (1, 1947)
- Lands, Alonzo M., M.A., Ph.D. Frederick Stearns and Co., 6533 Jefferson Ave., Detroit, Mich. *Director, Pharmacologic Research* (1, 1942, 3, 1947)
- Lange, Carl, M.D. 371 Morris St., Albany, N. Y. *Associate Bacteriologist, Divisions of Laboratories and Public Health, New York State Department of Health* (6, 1938)
- Langley, Wilson D., Ph.D. University of Buffalo Medical School, Buffalo, N. Y. *Professor of Biochemistry* (2, 1937)
- Langworthy, Orthello R., M.A., M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Psychiatry, Johns Hopkins University* (1, 1928)
- Lardy, Henry A., M.S., Ph.D. Dept. of Biochemistry, University of Wisconsin, Madison 6, Wis. *Assistant Professor* (2, 1946)
- Larrabee, Martin G., Ph.D. Johnson Foundation, for Medical Physics, University of Pennsylvania, Philadelphia. *Associate Professor of Biophysics* (1, 1940)
- Larson, Edward, Ph.D. Temple University Medical School, Broad and Ontario Sts., Philadelphia, Pa. *Associate Professor of Pharmacology* (1, 1929, 3, 1937)
- Larson, Hardy W., A.M., Ph.D. Metropolitan Life Insurance Co., Biochemical Laboratory, 1 Madison Ave., New York City. *Research Chemist* (2, 1937)
- Larson, Paul S., Ph.D. Medical College of Virginia, Richmond. *Associate Professor of Research Pharmacology* (1, 1939, 3, 1947)
- Lashley, K. S., M.S., Ph.D., D.Sc. Yerkes Laboratories, Orange Park, Fla. *Research Professor of Neuropsychology, Harvard University, Director, Yerkes Laboratories of Primate Biology, Inc. Member of the National Academy of Sciences* (1, 1923)
- Laskowski, M., Ph.D. Marquette University Medical School, Milwaukee 3, Wis. *Associate Professor of Biochemistry* (2, 1944)
- Lauffer, Max A., Jr., M.S., Ph.D. 307 Thaw Hall, University of Pittsburgh, Pittsburgh, Pa. *Research Professor* (2, 1946)
- Laug, E. P., M.A., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Senior Pharmacologist* (2, 1938, 3, 1947)
- Lauson, Henry D., Ph.D., M.D. The Rockefeller Institute, 66th St. & York Ave., New York 21, N. Y. *Associate* (1, 1946)
- Lavine, T. F., Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Chemist* (2, 1938)
- Lawrence, W. Sherwood, M.D. Permanente Foundation Hospital, 280 MacArthur Boulevard, West Oakland 11, Calif. (3, 1944)
- Lawson, Hampden, M.D., Ph.D. University of Louisville, Louisville, Ky. *Professor of Physiology* (1, 1933)
- Leake, Chauncey D., M.S., Ph.D. The University of Texas Medical Branch, Galveston. *Vice-*

- President of the University of Texas in Charge of the Medical Program* (1, 1923, 3, 1924)
- Leatham, James H, Ph D Rutgers University, New Brunswick, N J *Assistant Professor of Zoology* (1, 1945)
- Leathes, John Beresford, M A, M B, F R C S, F R S Westfield Warr Lane, Lyme Regis, Dorset, England (2, 1909)
- Lederer, Ludwig George, Ph D, M D Pennsylvania Central Airlines, National Airport, Washington, D C *Medical Director* (1, 1940)
- Lee, Milton O, M A, Ph D 2101 Constitution Ave, Washington 25, D C *Executive Secretary and Managing Editor, American Physiological Society* (1, 1927, 5, 1933)
- Leese, Chester E, M S, Ph D George Washington University School of Medicine, Washington, D C *Associate Professor of Physiology* (1, 1934)
- Lehman, Arnold J, Ph D, M D Food and Drug Administration, Washington 25, D C *Chief, Division of Pharmacology* (3, 1937)
- Lehman, Robert A, M S, Ph D New York University College of Medicine, 477 First Ave, New York City *Instructor in Therapeutics* (3, 1942)
- Lehmann, Gerhard, M D, Dr Ing Pharmacology Department, Hoffmann-La Roche, Nutley 10, N J *Pharmacologist* (3, 1939)
- Lehninger, Albert L, M S, Ph D University of Chicago Medical School, Chicago, Ill *Assistant Professor of Biochemistry in the Depts of Biochemistry and Surgery* (2, 1946)
- Lehr, David, M D New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave at 105th Street, New York 29, N Y *Assistant Professor of Pharmacology* (3, 1947)
- Leimdorfer, Alfred, M D Department of Psychiatry, University of Illinois College of Medicine, Chicago 12 *Associate Professor* (1, 1947)
- Lein, Allen, B A, M A, Ph D Department of Physiology, Northwestern University Medical School, Chicago 11, Ill *Physiologist* (1, 1946)
- Lenhart, Carl H, M D Lakeside Hospital, 2065 Adelbert Rd, Cleveland, O *Oliver H Payne Professor of Surgery, Western Reserve University* (1, 1921)
- Lennette, Edwin H, Ph D, M D Virus Laboratory, 1392 University Ave, Berkeley 2, Calif (4, 1941, 6, 1947)
- Leonard, Clifford Shattuck, M S, Ph D Lakeside Laboratories, Inc, Milwaukee 1, Wis *Chief, Biological Division* (3, 1927)
- Lepkovsky, Samuel, M S, Ph D University of California, Berkeley *Associate Professor of Poultry Husbandry* (2, 1933, 5, 1933)
- L'Esperance, Elise L, M D 2 East 61st St, New York, N Y *Director, Strong Cancer Prevention Clinic, Memorial Hospital, and New York Infirmary* (6, 1920)
- Leverson, Ruth M, Ph D Department of Home Economics, University of Nebraska, Lincoln *Associate Professor Human Nutrition Research* (5, 1942)
- Levin, Louis, Ph D College of Physicians and Surgeons, Columbia Univ, 630 W 168th St, New York 32, N Y *Assistant Professor of Anatomy* (2, 1939)
- Levine, Harold, Ph D Pabst Brewing Co, 917 W Juneau Ave, Milwaukee, Wis *Biochemist* (2, 1933, 5, 1933)
- Levine, Milton, M S, Ph D Inst of Experimental Medicine, College of Medical Evangelists, 312 N Boyle Ave, Los Angeles, Calif (6, 1942)
- Levine, Philip, M A, M D, F A C P Ortho Research Foundation, Ritten, N J *Director, Biologic Division* (6, 1925)
- Levine, Rachmiel, M D, C M Michael Reese Hospital, Chicago, Ill *Acting Director, Department of Metabolic Research Professorial Lecturer in Physiology, University of Chicago* (1, 1942)
- Levine, Samuel Z, M D, New York Hospital, 525 E 68th St, New York City *Professor of Pediatrics, Cornell University Medical College, Pediatrician-in-Chief, New York Hospital* (5, 1933)
- Levine, Victor Emanuel, A M, Ph D, M D Creighton University School of Medicine, Omaha, Neb *Professor of Biological Chemistry and Nutrition* (2, 1936)
- Levinson, Samuel A, Ph D, M D University of Illinois College of Medicine, 808 S Wood St, Chicago *Professor of Pathology, Director Laboratories, Research & Educational Hospital* (4, 1938)
- Levison, Louis A, M D 421 Michigan St, Toledo, O *Physician to Toledo Hospital, Physician to St Vincent Hospital* (6, 1916)
- Levy, Milton, Ph D 477 First Ave, New York City *Associate Professor of Chemistry, New York University College of Medicine* (2, 1933)
- Levy, Robert L, M D 730 Park Ave, New York City *Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University* (3, 1915)
- Lewey, F H, M D 3400 Spruce St, Philadelphia 4, Pa *Professor of Neuroanatomy, University of Pennsylvania Graduate School of Medicine, Associate in Neuropathology and Neurosurgery, Medical School* (1, 1937)
- Lewis, Gladys Kinsman, M A, Ph D 401 S Lafayette St, Denver 9, Colo (5, 1944)
- Lewis, Howard Bishop, Ph D Medical School, University of Michigan, Ann Arbor *Professor of Biological Chemistry* (1, 1925, 2, 1913, 5, 1933)

- Lewis, James C, M S, Ph D Western Regional Research Laboratory, U S Dept of Agriculture, Albany 6, Calif *Associate Biochemist* (2, 1916)
- Lewis, Julian Herman, M D 1750 Champlain Ave, Chicago, Ill *Associate Professor of Pathology, University of Chicago, Member of the Otto S A Sprague Memorial Institute* (1, 1924)
- Lewis, Lena A, A B, M A, Ph D Cleveland Clinic, Euclid Ave & E 93rd St, Cleveland 6, Ohio *Research Staff* (1, 1916)
- Lewis, Robert C, Ph D 4200 E 9th Ave, Denver, Colo *Professor of Biochemistry, School of Medicine, University of Colorado* (2, 1931, 5, 1933)
- Lewis, Warren H, M D The Wistar Institute of Anatomy and Biology, Woodland Ave and 36th St, Philadelphia, Pa *Member, Member of the National Academy of Sciences* (1, 1919)
- Li, Choh Hao, Ph D 4596 Life Science Bldg, University of California, Berkeley *Associate Professor of Experimental Biology* (2, 1914)
- Li, Richard C, M D National Peking University College of Medicine, Peiping, China (3, 1911)
- Libby, Raymond L, M S, Ph D American Cyanamid Co, 1937 W Main St, Stamford, Conn *Bio-physicist* (6, 1935)
- Libet, Benjamin, Ph D Univ of Chicago, Chicago 37, Ill *Assistant Professor of Physiology* (1, 1942)
- Liddell, Howard S, A M, Ph D Cornell University, Ithaca, N Y *Professor of Psychology* (1, 1925)
- Lieb, Charles C, M D 630 W 168th St, New York City *Hosack Professor of Pharmacology, College of Physicians and Surgeons Columbia University* (1, 1936, 3, 1915)
- Lieberman, Arnold L, M D, Ph D 328 No Country Club Road, Tucson, Ariz (1, 1934)
- Lifson, Nathan, M D, Ph D 617 Kenwood Parkway, Minneapolis, Minn *Associate Professor of Physiology, University of Minnesota Medical School* (1, 1944)
- Lightbody, Howard D, M S, Ph D Western Regional Research Laboratory, U S Department of Agriculture, Albany 6, Calif *Principal Biochemist* (2, 1936)
- Lihenthal, Joseph L, Jr, M D Johns Hopkins Hospital, Baltimore 5, Md *Associate Professor of Medicine* (1, 1945)
- Lillie, Ralph Stayner, Ph D, Sc D University of Chicago, Chicago, Ill *Professor Emeritus of General Physiology, Physiologist, Marine Biological Laboratory, Woods Hole, Mass* (1, 1905, 2, 1913)
- Lillie, R D, M D Chief Pathology Laboratory, National Institute of Health, Bethesda, Md *Medical Director, U S P H S* (4, 1941)
- Lim, Robert Kho-Seng, Ph D, D Sc, F R S E Peiping Union Medical College, Peiping, China *Professor of Physiology* (1, 1923)
- Lindsley, Donald B, M A, Ph D Dept of Psychology, Northwestern Univ, Evanston, Ill *Professor of Psychology* (1, 1937)
- Linegar, Charles R, Ph D E R Squibb and Sons, Biological Laboratory, New Brunswick, N J *Chief, Biological Development and Control Laboratory* (3, 1938)
- Lineweaver, Hans, M A, Ph D Western Regional Research Laboratory, U S Department of Agriculture, Albany 6, Calif *Senior Biochemist* (2, 1941)
- Link, Karl Paul, Ph D Biochemistry Building, University of Wisconsin, Madison *Professor of Biochemistry* (2, 1931)
- Lintz, William, M D 36 Plaza St, Brooklyn, N Y *Late Professor of Immunology and Bacteriology and Clinical Professor of Medicine, Long Island College of Medicine* (6, 1920)
- Lipman, Mrs Miriam O, A M Presbyterian Hospital, 620 W 168th St, New York City *Research Assistant, Edward Daniels Faulkner Arthritis Clinic* (6, 1931)
- Lipmann, Fritz, M D, Ph D Biochemical Research Laboratory, Massachusetts General Hospital, Boston *Research Chemist, Head, Biochemical Research Laboratory, Research Fellow in Biochemistry and Surgery, Harvard Medical School* (2, 1941)
- Lippincott, Stuart W, M D University of Washington School of Medicine, Seattle, Wash *Chairman, Department of Pathology* (4, 1947)
- Lipschitz-Lindley, Werner, Ph D, M D Lederle Laboratories, Pearl River, N Y *Research Pharmacologist* (3, 1947)
- Lipton, Morris A, Ph D 5645 S Maryland Ave, Chicago 37, Ill *Research Associate in Medicine, University of Chicago* (2, 1946)
- Lisco, Hermann, M D Argonne National Laboratory, Chicago 8, Ill *On leave from Harvard* (4, 1947)
- Litchfield, John T, Jr, M D American Cyanamid Co, 1937 W Main St, Stamford, Conn *Director of Pharmacology* (3, 1940)
- Little, James Maxwell, M S, Ph D Bowman Gray School of Medicine of Wake Forest College, Winston Salem, N C *Associate Professor of Physiology and Pharmacology* (1, 1942, 3, 1947)
- Livingston, Alfred E, Ph D Temple University School of Medicine, Philadelphia, Pa *Professor of Pharmacology* (1, 1917, 3, 1920)
- Lloyd, David P C, D Ph Rockefeller Inst for Medical Research, 66th St and York Ave, New York 21, N Y *Associate Member* (1, 1939)
- Locke, Arthur P, Ph D Zonite Products Corporation, New Brunswick, N J *Chief Research Chemist* (6, 1926)

- Lodholz, Edward, M D Medical Laboratories, University of Pennsylvania, Philadelphia *Emeritus Professor of Physiology, Graduate School of Medicine* (1, 1913)
- Loeb, Leo, M D Washington University Medical School, St Louis, Mo *Professor Emeritus of Pathology, Member, National Academy of Sciences* (1, 1907, 4, 1913)
- Loebel, Robert O, M D Russell Sage Institute of Pathology, Cornell Medical College, 1300 York Ave, New York City *Research Fellow, Adjunct Assistant Visiting Physician, Second (Cornell) Medical Division of Bellevue Hospital* (1, 1928)
- Loew, Earl R, M S, Ph D Univ of Ill College of Med, 1853 W Polk St, Chicago 12 *Associate Professor of Pharmacology* (1, 1940, 3, 1916)
- Loewe, W S, M D Department of Pharmacology, University of Utah School of Medicine, Salt Lake City 1 (3, 1936)
- Logan, Milan A, Ph D University of Cincinnati School of Medicine, Cincinnati, O *Professor of Biological Chemistry* (2, 1936)
- Long, C N H, M Sc, D Sc, M D Yale University, New Haven, Conn *Sterling Professor of Physiological Chemistry* (1, 1935, 2, 1927)
- Long, Esmond R, M D 7th and Lombard Sts, Philadelphia, Pa *Director, Henry Phipps Institute, Professor of Pathology, University of Pennsylvania* (4, 1930)
- Long, Perrin Hamilton, M D The Johns Hopkins University, 615 N Wolfe St, Baltimore, Md *Professor of Preventive Medicine, Colonel, M C* (3, 1940)
- Longcope, Warfield T, M D Cornhill Farm, Lee, Mass (3, 1921, 4, 1913, 6, 1923)
- Longenecker, Herbert Eugene, M S, Ph D University of Pittsburgh, Pittsburgh, Pa *Dean the Graduate School and Professor of Biochemistry* (2, 1940, 5, 1945)
- Longwell, Bernard B, M S, Ph D 1200 East 9th Ave, Denver 7, Colo *Associate Professor of Biochemistry, Univ of Colorado, School of Medicine* (2, 1946)
- Looney, Joseph M, M D 75 Park St, West Roxbury, Mass *Director of Laboratories, V A Hospital, West Roxbury, Mass* (2, 1922)
- Loosli, Clayton Garr, M D, University of Chicago, Chicago, Ill *Associate Professor of Medicine* (4, 1940)
- Loosli, J K, M S, Ph D Animal Nutrition Laboratory, Cornell University, Ithaca N Y *Assoc Prof of Animal Nutr and Assoc Animal Nutritionist in Exp Sta* (5, 1944)
- Lorber, Victor, M D, Ph D Dept of Biochemistry, Western Reserve Univ School of Medicine, Cleveland, Ohio *Associate Professor* (1, 1944)
- Lorente de N6, Rafael, M D The Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Member* (1, 1937)
- Lorenz, Egon, Ph D National Cancer Institute, Bethesda, Md *Biophysicist* (4, 1912)
- Loring, H S, M A, Ph D Stanford University, Calif *Professor of Biochemistry* (2, 1938)
- Loveless, Mary H, M D New York Hospital, 525 E 68th St, New York City *Research Associate, Cornell Medical School, Physician to Out-Patients, New York Hospital* (6, 1911)
- Lowell, Francis C, M D Nine Acre Corner, Concord, Mass *Instructor in Medicine, Boston City Hospital* (6, 1912)
- Lowenbach, Hans, M D Duke University Medical School, Durham, N C *Associate Professor of Neuropsychiatry and Physiology* (1, 1946)
- Lowry, Oliver H, M D, Ph D Washington University School of Medicine, 4580 Scott Ave, St Louis 10, Mo *Professor of Pharmacology and Head of Department* (2, 1912)
- Lubinski, Herbert, M D Jewish General Hospital, 3755 St Catherine Rd, Montreal, Canada *Bacteriologist* (6, 1911)
- Lucas, Colin C, M A Sc, Ph D Banting and Best Dept of Medical Research, University of Toronto, Toronto, Canada *Associate Professor* (2, 1916)
- Lucas, George H W, M A, Ph D University of Toronto, Toronto, Canada *Associate Professor of Pharmacology* (2, 1925, 3, 1928)
- Luck, James Murray, Ph D Stanford University, Stanford, Calif *Professor of Biochemistry* (2, 1925)
- Lucké, Balduin, M D 111 Montgomery Ave, Bala-Cynwyd, Pa *Professor of Pathology, University of Pennsylvania Medical School* (4, 1924)
- Luckhardt, Arno Benedict, M S, Ph D, M D, Sc D, LL D University of Chicago, Chicago, Ill *Professor of Physiology* (1, 1911)
- Ludewig, Stephan, Ph D University of Virginia School of Medicine, University Station, Charlottesville *Associate Professor of Biochemistry* (2, 1911)
- Ludena, Froilan P, Ph D, M D Sterling-Winthrop Research Institute, Rensselaer, N Y (3, 1911)
- Lukens, Francis D W, M D University of Pennsylvania, 809 Maloney Clinic, 36th and Spruce Sts, Philadelphia *Assistant Professor of Medicine and Director, George S Cox Medical Research Institute* (1, 1938)
- Lund, E J, Ph D Department of Zoology and Physiology, University of Texas, Austin *Professor of General Physiology* (1, 1930)
- Lundgren, Harold P, Ph D Western Regional Research Laboratory, U S D A, Albany 6, Calif *Senior Chemist* (2, 1942)
- Lundy, John Silas, M D The Mayo Foundation,

- Rochester, Minn *Chief of Section on Anesthesia* (3, 1935)
- Lurie, Max B, M D Henry Phipps Institute, 7th and Lombard Sts, Philadelphia, Pa *Associate Professor of Experimental Pathology* (4, 1931, 6, 1930)
- Lutz, Brenton R, Ph D Boston University, 688 Boylston St, Boston, Mass *Professor of Biology* (1, 1925)
- Luyet, Basile J, Sc D (Biol), Sc D (Physics) St Louis University School of Medicine, St Louis, Mo *Professor of Biology* (1, 1936)
- Lyall, Harold W, A M, Ph D Division of Laboratories and Research, New York State Department of Health, Albany *Assistant Director in charge of Antitoxin, Serum, and Vaccine Laboratories* (6, 1937)
- Lyman, Carl M, A M, Ph D A and M College of Texas, College Station *Professor of Biochemistry and Nutrition* (2, 1940)
- Lyman, John F, Ph D Townsend Hall, Ohio State University, Columbus *Professor of Agricultural Chemistry* (2, 1920, 5, 1933)
- Maaske, Clarence A, Ph D University of Colorado School of Medicine, 4200 E 9th Ave, Denver, Colo *Associate Professor of Physiology and Pharmacology* (1, 1945)
- Macallum, A Bruce, M D, Ph D Medical School, University of Western Ontario, London, Ont, Canada *Professor of Biochemistry* (2, 1914)
- MacArthur, Edith H, A M, Ph D Skidmore College, Saratoga Springs, N Y *Professor and Director of Home Economics* (5, 1933)
- MacCorquodale, D W, M S, Ph D Abbott Laboratories, North Chicago, Ill *Head, Biochemical Research* (2, 1934)
- MacFadyen, Douglas A, M A, M D Rush-Presbyterian Hospital Division, University of Illinois College of Medicine, 1753 West Congress St, Chicago 12, Ill *Professor of Biochemistry* (2, 1942)
- Macht, David Israel, M D, Ph D (hon), Litt D Sinai Hospital, Baltimore, Md *Research Pharmacologist, Sinai Hospital Laboratories, and Consultant Pharmacologist, Sinai Hospital* (1, 1916, 3, 1915)
- MacKay, Eaton M, M D The Scripps Metabolic Clinic, La Jolla, Calif (1, 1930)
- Mackenzie, Cosmo G, A B, Sc D Dept of Biochemistry, Cornell Univ Med College, 1300 York Ave, New York 21, N Y *Assistant Professor* (1, 1946, 2, 1946, 5, 1942)
- Mackenzie, George M, M D Mary Imogene Bassett Hospital, Cooperstown, N Y *Physician in Chief, Director, Otsego County Laboratories* (6, 1921)
- MacLeod, Colin M, M D New York University College of Medicine, 177 First Ave, New York City *Professor of Bacteriology* (6, 1937)
- MacLeod, Florence L, M A, Ph D University of Tennessee, Knoxville *Professor of Nutrition* (2, 1927, 5, 1933)
- MacLeod, Grace, M A, Ph D 106 Morningside Drive New York City *Professor Emeritus of Nutrition Teachers College, Columbia University* (2, 1924, 5, 1933)
- MacLeod, John, M S, Ph D Cornell University Medical College, 1300 York Ave New York City *Assistant Professor of Anatomy* (1, 1942)
- MacNabb, Andrew L, V S, B V Sc, F A P H A Department of Health of Ontario, Toronto, Canada *Director of Laboratories* (6, 1941)
- MacNider, William deB, M D, Sc D, LL D University of North Carolina, Chapel Hill *Kennan Research Professor of Pharmacology, Member, National Academy of Sciences* (1, 1912, 2, 1912, 3, 1909, 4, prior to 1920)
- MacPherson, Catherine F C, M Sc, Ph D McGill University, 4961 Coronet Avenue, Montreal, Quebec, Canada *Research Fellow* (2, 1947)
- MacPhillamy, Betty Bowser, M S, Ph D 35 Beckman Rd, Summit, N J *Virologist* (6, 1944)
- Madden, Sidney C, M D Emory University, School of Medicine, Atlanta, Ga *Professor of Pathology* (4, 1939)
- Maddock, Stephen, M D Boston City Hospital, Boston, Mass *Director of Surgical Research Laboratory, Assistant Professor of Surgery, Tufts Medical School* (4, 1931)
- Madsen, Louis L, Ph D Dept of Animal Husbandry, Utah State Agricultural College, Logan *Nutritionist* (5, 1940)
- Magath, Thomas B, M S, Ph D, M D Mayo Clinic, Rochester, Minn *Associate Professor of Clinical Bacteriology and Parasitology, University of Minnesota, Mayo Foundation, Consultant Physician in Clinical Laboratories, Mayo Clinic* (1, 1928)
- Magill, Thomas P, M D Cornell University Medical College, 1300 York Ave, New York City (6, 1937)
- Magoun, Horace W, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill *Professor of Microscopic Anatomy* (1, 1937)
- Mahon, Eleanor Conway, Ph D Iron River, Mich (4, 1940)
- Mann, Roland J, Ph D Eaton Laboratories, Inc, Eaton Ave, Norwich, N Y (1, 1936)
- Maison, George L, M S, M D Boston University Medical School, 80 E Concord St, Boston 18, Mass *Professor of Pharmacology* (1, 1939)
- Major, Randolph T, M Sc, Ph D Coles Ave,



- Mountainside, Westfield, N J *Director of Research, Merck & Co, Inc, Rahway, N J* (2, 1942)
- Mallory, G Kenneth, M D *Mallory Institute of Pathology, Boston City Hospital, Boston, Mass Professor* (4, 1940)
- Mallory, Tracy B, M D *Massachusetts General Hospital, Boston Director of Pathology and Bacteriology, Assistant Professor of Pathology, Harvard Medical School* (4, 1937)
- Maloney, Arnold H, Ph D, M D, LL D *Howard University School of Medicine, Washington, D C Professor and Head of Department of Pharmacology* (3, 1932)
- Maltaner, Frank, Ph D 388 New Scotland Ave, Albany, N Y *Associate Biochemist, Division of Laboratories and Research, New York State Department of Health* (6, 1920)
- Maluf, N S Rustum, M S, Ph D 101 W Chestnut St, Louisville 2, Ky (1, 1942)
- Man, Evelyn B, Ph D 333 Cedar St, New Haven, Conn *Assistant Professor in the Biochemistry Laboratory, Dept of Psychiatry, Yale University School of Medicine* (2, 1936)
- Manery, Jeanne Forest, M A, Ph D *Medical School, University of Toronto, Toronto, Ont, Canada Demonstrator in Biochemistry* (1, 1937)
- Mangun, George H, Ph D 15713 Heyden, Detroit, Mich (2, 1947)
- Mann, Frank C, M A, M D, Sc D, LL D *Mayo Clinic, Box 256, Rochester, Minn Director, Division of Experimental Medicine, Professor of Experimental Medicine, Mayo Foundation* (1, 1916, 3, 1923, 4, 1924)
- Manning, G W, M D 20 Woodington Ave, Toronto, Ontario, Canada *Medical Officer in Charge, No 2 R C A F Research Unit* (1, 1944)
- Manville, Ira Albert, M A, M D, Ph D 811 N W 19th Ave, Portland 9, Ore (1, 1933)
- Manwaring, Wilfred H, M D *Stanford University, Palo Alto, Calif Professor Emeritus of Bacteriology and Experimental Pathology* (1, prior to 1920, 6, 1917)
- Marine, David, A M, M D 18 Baltimore Ave, Rehoboth, Del (1, 1910, 4, 1913)
- Markee, Joseph E, Ph D *Duke University School of Medicine, Durham, N C Professor of Anatomy* (1, 1945)
- Markowitz, J, M D, Ph D 220 Bloor St, Toronto, Ont, Canada *Research Associate in Physiology, University of Toronto, Faculty of Medicine* (1, 1929)
- Marmont, George H, Ph D *Institute of Radiobiology and Biophysics, University of Chicago, Chicago 37, Ill, Assistant Professor of Physiology* (1, 1941)
- Marmorston, Jessie 116 N Bedford Drive Beverly Hills, Calif (6, 1932)
- Marrazzi, Amedeo S, M D *Wayne University College of Medicine, Detroit 26, Mich Professor and Head of the Department of Pharmacology* (3, 1938)
- Marsh, David F, A B, M S, Ph D *Dept of Pharmacology, West Virginia University, Morgantown, W Va Head and Associate Professor of Pharmacology* (3, 1916)
- Marsh, Gordon, Ph D *State University of Iowa, Iowa City, Associate Professor of Zoology* (1, 1911)
- Marsh, M Elizabeth, M S, Ph D *Kilham Research Laboratories, 19 W 15th St, New York City Assistant Director* (1, 1929, 5, 1933)
- Marshak, Alfred Gordon, M A, Ph D *Tuberculosis Control Division, U S Public Health Service, Washington 11, D C* (1, 1910)
- Marshall, Eli Kennerly, Jr, Ph D, M D, LL D *Johns Hopkins Medical School, Baltimore, Md Professor of Pharmacology and Experimental Therapeutics Member, National Academy of Sciences* (1, 1915, 2, 1913, 3, 1915)
- Marshall, Louise Hanson, M A, Ph D *Laboratory of Physical Biology, Natl Inst of Health, Bethesda, Md Associate Physiologist* (1, 1916)
- Marshall, Wade H, Ph D 9700 Brunett Ave, Silver Spring, Md *Physicist, Applied Physics Laboratory, Johns Hopkins University* (1, 1937)
- Martin, Arthur W, Jr, Ph D *Physiology Hall, University of Washington, Seattle Associate Professor of Physiology* (1, 1914)
- Martin, Donald S, M D *Duke Hospital, Durham, N C Associate Professor of Bacteriology and Associate in Medicine, Professor of Preventive Medicine and Public Health, Duke University School of Medicine* (4, 1940, 6, 1943)
- Martin, Foster N, Jr, Ph D, M D *Department of Pharmacology, Tulane University Medical School, P O Station 20, New Orleans, La Assistant Professor* (3, 1947)
- Martin, Stephens J, M A, Ph D *St Francis Hospital, Hartford, Conn* (1, 1933)
- Mason, Edward C, M D, Ph D *University of Oklahoma School of Medicine, Oklahoma City Professor of Physiology* (1, 1935)
- Mason, Eleanor Dewey, A B, A M, Ph D *Dept of Physiology and Nutrition, Women's Christian College, Cathedral P O, Madras, India Professor of Physiology and Nutrition* (1, 1946)
- Mason, H L, M A, Ph D *Mayo Clinic, Rochester, Minn Associate Professor of Physiological Chemistry, The Mayo Foundation, University of Minnesota* (2, 1941)
- Mason, Karl Ernest, Ph D *The University of Rochester, School of Medicine and Dentistry,*

- Rochester, N Y *Professor of Anatomy* (5, 1941)
- Mason, Morton F, Ph D Parkland Hospital, Oak Lawn Ave, Dallas, Texas *Professor of Pathological Chemistry and Experimental Medicine, Southwestern Medical College* (2, 1938)
- Massengale, Oliver N, Ph D Mead Johnson & Co, Research Laboratory, Evansville, Ind *Research Biochemist* (2, 1937)
- Masson, Georges M C, Ph D 388 West St Paul St, Montreal, Canada (1, 1944)
- Mathews, Albert Prescott, Ph D, D Sc (hon) Woods Hole, Mass *Professor Emeritus of Biochemistry, Univ of Cincinnati* (1, 1898, 2, 1906)
- Mattill, Henry A, A M, Ph D State University of Iowa, Iowa City *Professor and Head of Department of Biochemistry* (1, 1913, 2, 1909, 5, 1933)
- Mattis, Paul A, B S, D Sc School of Pharmacy, Univ of Florida, Gainesville, Fla *Head Professor of Pharmacognosy and Pharmacology* (3, 1946)
- Maurer, Frank W, Ph D 301 Lake Ave, Newton Highlands 61, Mass (1, 1941)
- Mautz, Frederick R, M D Western Reserve School of Medicine, Cleveland 6, O *Assistant Professor of Surgery* (1, 1945)
- Maver, Mary E, Ph D National Cancer Institute, Bethesda 14, Md *Senior Biochemist* (2, 1947)
- Mavor, James Watt, Ph D 8 Gracewood Park, Cambridge, Mass (1, 1930)
- Maxfield, Mary E, A M, Ph D Department of Pharmacology, Wayne University College of Medicine, Detroit 26, Mich *Research Associate* (1, 1947)
- Mayer, Manfred M, Ph D 1739 Eutaw Place, Baltimore, Md *Instructor in Biochemistry* (6, 1946)
- Mayerson, Hymen S, Ph D Tulane University School of Medicine, Station 20, New Orleans, La *Professor of Physiology and Head of Dept of Physiology* (1, 1928)
- Maynard, Leonard A, Ph D, Sc D Cornell University, Ithaca, N Y *Professor of Nutrition and Biochemistry, Director, School of Nutrition, Member National Academy of Sciences* (2, 1930, 5, 1933)
- Mazur, Abraham, M A, Ph D College of the City of New York, 139th St and Convent Ave, *Instructor* (2, 1944)
- McCann, William S, M D, D Sc (Hon) University of Rochester, School of Medicine, Rochester, N Y *The Charles A Deacy Professor of Medicine* (2, 1923, 5, 1933)
- McCarrell, June D Department of Biology, Hood College, Frederick, Md (1, 1942)
- McCarty, Maelyn, M D 66th Street and York Avenue, New York 21, N Y *Associate, Rockefeller Institute for Medical Research* (6, 1947)
- McCawley, Elton Leeman, Ph D Yale Medical School, New Haven, Conn *Instructor in Pharmacology* (3, 1944)
- McCay, Clive M, M S, Ph D Animal Nutrition Laboratory, Dairy Building, Cornell University, Ithaca, N Y *Professor of Nutrition* (2, 1929, 5, 1933)
- McChesney, Evan Wilham, Ph D Ladox Laboratories, Inc, 2 Vine St, Philadelphia, Pa (1, 1944)
- McClellan, Walter S, M D Saratoga Spa, Saratoga Springs, N Y *Medical Director, Associate Professor of Medicine, Albany Medical College* (1, 1931)
- McClendon, J F, M S, Ph D Route 1, Box 383, Trooper Road, Norristown, Pa *Research Professor of Physiology, Hahnemann Medical College* (1, 1910, 2, 1914, 5, 1935)
- McClosky, William T, B A 5120 7th St, N W, Washington, D C *Senior Pharmacologist, Div of Pharmacology, Food and Drug Administration* (3, 1929)
- McCollum, Elmer Verner, M A, Ph D, Sc D, LL D Johns Hopkins University, Baltimore, Md *Emeritus Professor of Biochemistry, Member, National Academy of Sciences* (2, 1910, 5, 1933)
- McCollum, Ernestine Becker, M A, Johns Hopkins University, School of Hygiene, Baltimore 5, Md *Assistant Professor of Biochemistry* (5, 1938)
- McCouch, Grayson Prevost, M D University of Pennsylvania, Philadelphia *Assistant Professor of Physiology* (1, 1925)
- McCouch, Margaret Sunwalt, M S, Ph D University of Pennsylvania Medical School, Philadelphia 4 (1, 1934)
- McCrea, Forrest D, Ph D Duke University School of Medicine, Durham, N C *Associate Professor of Physiology and Pharmacology* (1, 1929, 3, 1937)
- McCrudden, F H, M D 501 Boylston St, Boston, Mass *Assistant Medical Director, New England Mutual Life Insurance Co* (2, 1906)
- McCullagh, D Roy, M Sc (Man), Ph D (Cantab), FIC 150 Northfield Rd, Bedford, O (2, 1932)
- McCulloch, Warren Sturgis, M A, M D University of Illinois, College of Medicine, 912 S Wood St, Chicago *Associate Professor of Psychiatry* (1, 1936)
- McCutcheon, Morton, M D University of Pennsylvania Medical School, Philadelphia *Professor of Pathology* (4, 1925)
- McDonald, Francis Guy, M S, Ph D Research Laboratory, Mead Johnson & Co, Evansville,

- Ind *Assistant Director of Research* (2, 1936, 5, 1947)
- McElroy, L W Dept of Animal Science, University of Alberta Edmonton, Canada *Associate Professor of Animal Husbandry* (5, 1944)
- McElroy, William D, Ph D Dept of Biology, Johns Hopkins University, Baltimore, Md *Assistant Professor of Biology* (1, 1945)
- McEllroy, William Swindler, M D School of Medicine, University of Pittsburgh, Pittsburgh, Pa *Professor of Physiological Chemistry, Dean, School of Medicine* (2, 1919)
- McFarland, Ross A, Ph D Harvard University, Division of Industrial Research, Graduate School of Business Administration, Soldiers Field, Boston, Mass *Assistant Professor of Industrial Research* (1, 1943)
- McFarlane, William Douglas, Ph D 496 Queen St, E, Toronto, Canada *Director of Research, Canadian Breweries, Ltd* (2, 1933)
- McGinty, Daniel A, M A, Ph D Parke, Davis & Co, Detroit, Mich *Research Physiologist* (1, 1925)
- McGuigan, Hugh Alister, Ph D, M D 1853 W Polk St, Chicago, Ill *Professor of Pharmacology and Therapeutics, College of Medicine, University of Illinois* (1, 1907, 2, 1906, 3, 1913)
- McHargue, J S, M S, Ph D, D Sc Department of Chemistry, Kentucky Agricultural Experiment Station, University of Kentucky, Lexington *Emeritus Member* (2, 1927)
- McHenry, E W, M A, Ph D, F R S C School of Hygiene, University of Toronto, Toronto, Canada *Professor of Public Health Nutrition* (2, 1938, 5, 1935)
- McIntyre, A R, Ph D, M D College of Medicine, University of Nebraska, 42nd and Dewey Ave, Omaha *Professor of Physiology and Pharmacology* (1, 1933, 3, 1938)
- McKee, Clara M, Squibb Institute for Medical Research, New Brunswick, N J *Associate in Microbiology* (6, 1941)
- McKee, Frank W, M D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Veteran Postgraduate Fellow in Pathology* (4, 1947)
- McKee, Ralph Wendell, M S, Ph D Harvard Medical School, 25 Shattuck St, Boston, Mass *Assistant Professor of Biochemistry* (2, 1946)
- McLain, Paul L, M D University of Pittsburgh Medical School, Pittsburgh, Pa *Assistant Professor of Physiology and Pharmacology, Major, M C* (3, 1940)
- McLean, Franklin C, Ph D, M D University of Chicago, Chicago, Ill *Professor of Pathological Physiology* (1, 1914, 2, 1916, 3, 1916)
- McLean, I William, Jr, B S, M D Virus Research Division, Parke Davis Laboratory, Detroit, Mich *Senior Research Associate* (6, 1916)
- McLester, James S, M D, LL D University of Alabama, 930 S 20th St, Birmingham *Professor of Medicine* (5, 1933)
- McMaster, Philip D, M D The Rockefeller Institute for Medical Research, 66th St and York Ave, New York City (1, 1924)
- McMeekin, Thomas L, Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Philadelphia, Pa *Senior Chemist* (2, 1935)
- McNamara, Bernard P, M S, Ph D Pharmacology Section, Medical Division, Army Chemical Center, Md *Pharmacologist* (3, 1917)
- McNaught, James Bernard, M D University of Colorado School of Medicine, Denver 7 *Professor of Pathology* (4, 1936)
- McPhail, Murchie Kilburn, Ph D Vick Chemical Co, 35-22 Linden Place, Flushing, N Y *Chief Pharmacologist* (3, 1911)
- McQuarrie, Irvine, Ph D, M D University of Minnesota, Minneapolis *Professor and Head of Department of Pediatrics* (1, 1927, 5, 1933)
- McShan, W H, M A, Ph D Biology Building, University of Wisconsin, Madison 6, Wis *Associate Professor of Zoology* (2, 1917)
- Medes, Grace, Ph D Lankenau Hospital Research Institute, Philadelphia, Pa *Research Physiological Chemist* (2, 1930)
- Medlar, Edgar M, M D Path Bldg, Room 708 Bellevue Hospital, 1st Ave at 26th St, New York, N Y *Pathologist* (4, 1927)
- Meck, Walter J, Ph D University of Wisconsin, Madison *Professor of Physiology, Associate Dean of the Medical School, Member of National Academy of Sciences* (1, 1908)
- Mehl, John Wilbur, M A, Ph D Dept of Biochemistry, University of Southern California, Los Angeles, Calif *Professor of Biochemistry* (2, 1916)
- Mellon, Ralph R, M D, M Sc, Dr P H, Sc D (hon) Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh *Director* (6, 1918)
- Melnick, Daniel, Ph D Quartermaster Food and Container Institute for the Armed Forces, Chicago 9, Ill *Chief of the Food and Development Division* (2, 1940, 5, 1942)
- Melnick, Joseph L, Ph D Yale University School of Medicine, New Haven, Conn *Assistant Professor of Preventive Medicine* (2, 1946)
- Melville, Donald B, M S, Ph D Cornell University Medical College, 1300 York Avenue, New York 21, N Y *Assistant Professor of Biochemistry* (2, 1947)
- Melville, Kenneth Ivan, M Sc, M D, C M McGill University, Montreal, Canada *Assistant Professor of Pharmacology* (3, 1931)

- Mendel, Bruno, M D University of Toronto, 100 College Street, Toronto 5, Canada Professor of Cellular Physiology, Bunting Best Department of Medical Research (2, 1917)
- Mendenhall, Walter L, S M, M D 9 Acacia St., Cambridge, Mass Professor of Pharmacology, retired, Boston University Medical School (1, 1915, 3, 1917)
- Mendez, Rafael, M D National Institute of Cardiology, Calzada de la Piedad 300, Mexico D F, México Head of the Dept of Pharmacology (3, 1914)
- Mcneely, George R, M D Vanderbilt Univ School of Medicine, Nashville 1, Tenn Associate Professor of Medicine (1, 1916)
- Menkin, Vay, M A, M D Temple Univ School of Medicine, Philadelphia, Pa Associate Professor of Experimental Pathology (1, 1932, 4, 1932, 6, 1931)
- Menten, Maud L, M D, Ph D University of Pittsburgh, Pittsburgh, Pa Associate Professor of Pathology (1, 1915, 4, 1927)
- Mettler, Stacey R, M D University of California Hospital, San Francisco Associate Professor of Medicine (4, 1932)
- Mettler, Fred A, A M, Ph D, M D Department of Neurology, College of Physicians and Surgeons, Columbia University, New York City Associate Professor of Anatomy (1, 1937)
- Meyer, Curtis E, M S, Ph D The Upjohn Co., Kalamazoo, Mich Senior Research Chemist (2, 1942)
- Meyer, Karl, M D, Ph D 630 W 168th St., New York City Associate Professor of Biochemistry, Dept of Ophthalmology, College of Physicians and Surgeons, Columbia University (2, 1934)
- Meyer, Karl F, M D, Ph D Medical Center, San Francisco, Calif Professor of Bacteriology, University of California Director of the George Williams Hooper Foundation for Medical Research (1, 1930, 6, 1922)
- Meyerhof, Otto, M D, LL D Department of Physiological Chemistry, University of Pennsylvania School of Medicine, Philadelphia Research Professor of Biochemistry (2, 1941)
- Michaelis, Leonor, M D, LL D Rockefeller Institute for Medical Research, 66th St and York Ave., New York City Member Emeritus (2, 1929)
- Mickelsen, Olaf, Ph D University of Minnesota, Department of Physiological Hygiene, Stadium South Tower, Minneapolis Associate Professor (2, 1911)
- Mider, George Burroughs, M D Strong Memorial Hospital, Rochester 7, N Y Research Associate in Surgery (4, 1940)
- Miles, Walter R, A M, Ph D 333 Cedar St., New Haven, Conn Professor of Psychology, The School of Medicine and the Institute of Human Relations, Yale University, Member of the National Academy of Sciences (1, 1919)
- Millhorat, Ade T, M D Cornell University Medical College, 525 E 68th St., New York 21, N Y Associate Professor of Medicine, Research Fellow, Russell Sage Institute of Pathology (1, 1931, 3, 1937, 5, 1935)
- Miller, Augustus Taylor, Jr, Ph D University of North Carolina Medical School, Chapel Hill Associate Professor of Physiology (1, 1944)
- Miller, Benjamin F, Ch E, M D Dept of Medicine, Univ of Chicago, Chicago, Ill Assistant Professor of Medicine (2, 1938)
- Miller, Carey D, M S University of Hawaii, Honolulu Professor of Food and Nutrition, Hawaii Agricultural Experimental Station (5, 1942)
- Miller, C Phillip, M D, M S University of Chicago, Chicago, Ill Professor of Medicine (4, 1925, 6, 1923)
- Miller, Edgar C L, M D % Library, Medical College of Virginia, Richmond Directing Librarian (6, 1913)
- Miller, Edgar G, Jr, Ph D 630 W 168th St., New York City Professor of Biological Chemistry, Columbia University (2, 1930)
- Miller, Franklin R, M D Jefferson Medical College and Hospital, Division of Hematology, Philadelphia, Pa Associate Professor of Medicine (4, 1940)
- Miller, Frederick R, A M, M D, F R C P (C), F R S Faculty of Medicine, University of Western Ontario, London, Ont., Canada Research Professor of Neurophysiology (1, 1908)
- Miller, G H, M D American College of Surgeons, 40 E Erie St., Chicago 11, Ill Director of Educational Activities (3, 1925)
- Miller, H R, M D 1020 Park Ave., New York 28, N Y Montefiore Hospital, New York City (1, 1947)
- Miller, Leon L, Ph D, M D Jefferson Medical College, 1025 Walnut Street, Philadelphia 7, Penn Assistant Professor of Biochemistry (2, 1917)
- Miller, Lila, M S, Ph D Dept of Biological Chemistry, University of Michigan, Ann Arbor, Mich Assistant Professor of Biological Chemistry (2, 1946)
- Miller, Lloyd C, Ph D Sterling Winthrop Research Institute, 33 Riverside Ave., Rensselaer, N Y Director, Biology Division (3, 1938)
- Miller, R C, Ph D Pennsylvania State College, State College Assistant Professor Agricultural and Biological Chemistry (5, 1935)
- Miller, Zelma Baker, Ph D 1101 Trenton Place, S E, Washington, D C
- Mills, Clarence A, Ph D, M D Cincinnati General Hospital, Cincinnati 29, Ohio Pro-

- professor of *Experimental Medicine*, University of Cincinnati (1, 1921, 2, 1921)
- Minot, Annie Stone, Ph D Vanderbilt University Medical School, Nashville, Tenn *Research Associate, Department of Biochemistry* (1, 1923)
- Mirsky, Alfred E, Ph D Rockefeller Inst, 66th St and York Ave, New York 21, N Y *Associate Member* (2, 1941)
- Mirsky, I Arthur, M Sc, M D, C M The Jewish Hospital, Cincinnati, O *Director, The May Institute for Medical Research, Assistant Professor of Biochemistry, University of Cincinnati* (1, 1936)
- Mitchell, Harold H, M S, M D 120 S Lasky Dr, Beverly Hills, Calif (6, 1943)
- Mitchell, Harold H, M S, Ph D 557 Davenport Hall, University of Illinois, Urbana, Ill *Professor of Animal Nutrition* (2, 1919, 5, 1933)
- Mitchell, Helen S, Ph D University of Massachusetts, Amherst, Mass *Dean of the School of Home Economics* (2, 1925, 5, 1933)
- Mitchell, Philip H, Ph D Brown University Providence 12, R I *Robert P Brown Professor of Biology* (2, 1909)
- Modell, Walter, M D Cornell University Medical College, 1300 York Ave, New York, N Y *Instructor in Pharmacology* (3, 1944)
- Moe, Gordon Kenneth, Ph D, M D University of Michigan, Ann Arbor *Assistant Professor of Pharmacology* (3, 1944)
- Mohn, James F, M D 24 High St, Buffalo, N Y *Instructor in Bacteriology and Immunology, Univ of Buffalo School of Medicine* (6, 1946)
- Molitor, Hans, M D 50 Lawrence St, Rahway, N J *Director, Merck Institute for Therapeutic Research* (1, 1933, 3, 1942)
- Molomut, Norman, M A, Ph D Biological Labs, 16 Clinton St, Brooklyn 2, N Y (6, 1942)
- Moon, Virgil H, M Sc, M D Jefferson Medical College, Philadelphia, Pa *Professor of Pathology* (4, 1934)
- Moore, A R, Ph D University of Oregon, Eugene *Research Professor of General Physiology in the Department of Psychology* (1, 1912)
- Moore, Carl Vernon, M D Washington University School of Medicine, St Louis, Mo *Professor of Medicine* (4, 1938, 5, 1941)
- Moore, Lane A, Ph D Division of Nutrition and Physiology, Bureau of Dairy Industry, Beltsville, Md *Head, Section of Dairy Cattle Nutrition* (5, 1940)
- Moore, Robert A, M D Washington University Medical School, St Louis, Mo *Dean and Professor of Pathology* (4, 1929)
- Moore, Robert M, M D University of Texas Medical School, Galveston, Tex (1, 1932)
- Moorhouse, Victor Henry K, M B University of Manitoba, Winnipeg, Canada *Professor of Physiology* (1, 1912)
- Morehouse, Laurence E, M Ed, Ph D University of Southern California, Los Angeles 7 *Associate Professor* (1, 1947)
- Morgan, Agnes Fay, M S, Ph D University of California, Berkeley *Professor of Home Economics, Biochemist, Agric Exp Station* (2, 1929, 5, 1933)
- Morgan, Charles F, Ph D Georgetown University School of Medicine, Washington, D C *Professor of Physiology and Chairman of the Department of Physiology* (3, 1917)
- Morgan, Clifford T, M A, Ph D Psychology Department, Johns Hopkins University, Baltimore 18, Md (1, 1913)
- Morgulis, Sergius, A M, Ph D University of Nebraska College of Medicine, Omaha *Professor of Biochemistry* (1, 1914, 2, 1916)
- Morison, Robert S, M D Rockefeller Foundation, 66th St and York Ave, New York City *Assist Director of the Med Sciences* (1, 1938)
- Moritz, Alan R, M D Harvard Medical School, Boston, Mass *Professor of Legal Medicine* (4, 1934)
- Morrell, Clarence Allison, M A, Ph D Department of Pensions and National Health, Laboratory of Hygiene, Sussex and John Sts, Ottawa, Canada *Senior Pharmacologist* (3, 1937)
- Morris, Harold P, M S, Ph D National Cancer Institute, Bethesda, Md *Senior Nutrition Chemist, U S Public Health Service* (2, 1944, 5, 1943)
- Morris, Marion C Public Health Research Institute of City of New York, Foot of East 15th St, New York City *Associate in Division of Infectious Diseases* (6, 1936)
- Morrison, Dempsey B, M S, Ph D University of Tennessee College of Medicine, Memphis *Associate Professor of Chemistry* (2, 1936)
- Morrison, James L, Ph D Emory University School of Medicine, Emory University, Ga *Assistant Professor of Pharmacology* (3, 1944)
- Morse, Minerva, M S, Ph D 5525 Kimbark Ave, Chicago, Ill *Research Associate, Department of Pediatrics, University of Chicago* (2, 1934)
- Morse, Withrow, Ph D 32 Manchester Rd, Eastchester, via Tuckahoe, N Y *Consultant* (2, 1914)
- Mortimer, Bernard, Ph D, M D 25 N Ottawa St, Joliet, Illinois, Cook County Hospital, Chicago (1, 1936)
- Morton, John J, M D University of Rochester, School of Medicine and Dentistry, Rochester, N Y *Professor of Surgery* (4, 1927)
- Motley, H L Barton Memorial Division of Jefferson Medical College Hospital, Philadelphia 47, Pa (1, 1947)

- Moulton, C Robert, M S , Ph D 5602 Dorchester Ave , Chicago 37, Ill (5, 1933)
- Moxon, Alvin L , Ph D College Station, Brookings, S D Head, Chemistry Department, South Dakota Agricultural Experiment Station (2, 1941)
- Moyer, Carl A , Ph D 6117 Glenrose Ct , Dallas 1, Texas Southwestern Medical College, Dallas Professor of Experimental Surgery (1, 1943)
- Mudd, Stuart, M A , M D University of Pennsylvania, Philadelphia Professor of Bacteriology (1, 1921, 4, 1927, 6, 1927)
- Muehlberger, Clarence W , M S , Ph D State Health Department Laboratories Lansing, Mich State Toxicologist (3, 1928)
- Muclier, J Howard, M S , Ph D 2176 Centro St , W Roxbury, Mass Charles Wilder Professor of Bacteriology and Immunology, Harvard Medical School (2, 1922, 4, 1927, 6, 1920)
- Mukherji, B , M B , D Sc All-India Institute of Hygiene and Public Health, Calcutta Director, Biochemical Standardization Laboratory (3, 1938)
- Mulder, Arthur G , Ph D University of Tennessee College of Medicine, Memphis Associate Professor of Physiology (1, 1937)
- Mulinos, M G , M D , Ph D New York Medical College, Flower and Fifth Avenue Hospitals, Fifth Ave and 105th St , New York 29, N Y Associate Professor of Pharmacology (3, 1931)
- Mull, James W , Ph D 2020 State St , Quincy, Ill Associate, Quincy Specialties Co (2, 1937)
- Muller, Otto H , R N Dr Department of Physiology, Syracuse University College of Medicine, Syracuse 10, N Y (1, 1947)
- Mulligan, Richard M , M D University of Colorado School of Medicine, 4200 East 9th Avenue, Denver, Colo Associate Professor of Pathology (4, 1947)
- Mullin, F J , M S , Ph D Physiology Department, University of Chicago, Chicago 37, Ill Assistant Professor of Physiology (1, 1937)
- Munsell, Hazel E , M A , Ph D Nutrition Biochemistry Labs , Dept of Food Technology, Mass Inst of Technology, Cambridge Research Associate (5, 1933)
- Muntwyler, Edward, Ph D Long Island College of Medicine, 350 Henry St , Brooklyn, N Y Professor of Biochemistry (2, 1931)
- Murlin, John R , A M , Ph D , Sc D University of Rochester Medical School 260 Crittenden Blvd , Rochester, N Y Professor Emeritus of Physiology and Director Emeritus of Department of Vital Economics (1, 1906, 2, 1908, 5, 1933)
- Murphy, James B , M D Rockefeller Institute for Medical Research, 66th St and York Ave , New York City Member (4, prior to 1920)
- Murray, Everett G D , O B E , B A honors in Natural Science, M A , L M S S A , F R S C McGill University, Montreal, Canada Professor of Bacteriology and Immunology and Head of the Department, McGill University, Bacteriologist in-Chief to the Royal Victoria Hospital, to the Children's Memorial Hospital and to the Alexandra Hospital (6, 1933)
- Muus, Jytte, Mag Scient (Univ of Copenhagen), Mount Holyoke College, South Hadley, Mass Associate Professor (2, 1946)
- Myers, Chester N , Ph D , Sc D 34 Cedar Place, Yonkers 5, N Y Chief, Division Chemotherapy, N Y Skin and Cancer Hospital, Associate in Dermatology and Syphilology, College of Physicians and Surgeons, Research Chemist, Vanderbilt Clinic, Director, Chemical and Clinical Research, H A Metz Laboratories, Inc (2, 1922)
- Myers, Victor C , M A , Ph D , Sc D School of Medicine, Western Reserve University, Cleveland, O Professor and Director of Clinical Biochemistry (1, 1916, 2, 1910, 5, 1933)
- Nachmansohn, David, M D Dept of Neurology, College of Physicians and Surgeons, Columbia University, 630 W 168th St , New York City Research Associate in Neurology (1, 1940)
- Nadler, J Ernest, M D , Med D Sc 80-16 Lefferts Blvd , Kew Gardens 15, L I , N Y (3, 1940)
- Nahum, Louis N , M D 1142 Chapel St , New Haven, Conn Assistant Professor of Physiology, Yale University (1, 1934)
- Najjar, Victor A , M D Dept of Biological Chemistry, Washington Univ School of Medicine, St Louis, Mo (2, 1946)
- Nash, Thomas P , Jr , M A , Ph D 875 Monroe Ave , Memphis, Tenn Professor of Chemistry, College of Medicine, Dean of School of Biological Sciences, University of Tennessee (2, 1923)
- Nasset, Edmund S , M S , Ph D University of Rochester, 260 Crittenden Blvd , Rochester, N Y Associate Professor of Physiology (1, 1932, 5, 1940)
- Nathanson, Ira T , M S , M D Massachusetts General Hospital, Boston Instructor in Surgery, Harvard Medical School, Assistant in Surgery, Mass General Hospital (1, 1943)
- Nathanson, Morris D , M D 658 S Bonnie Brae St , Los Angeles, Calif Associate Clinical Professor of Medicine, University of Southern California School of Medicine (3, 1940)
- Neeheles, Heinrich, M D , Ph D Michael Reese Hospital, Chicago, Ill Director, Dept of Gastro-intestinal Physiology, Michael Reese Hospital, Professorial Lecturer in Physiology, University of Chicago (1, 1929)
- Neill, James M , Ph D Medical College, Cornell University, 1300 York Ave , New York City

- Professor of Bacteriology and Immunology* (6, 1930)
- Nelson, Charles Hugh A M , Ph D , M D Humboldt Building, St Louis, Mo *Associate Dean and Professor of Medicine, St Louis University Medical School* (2, 1906)
- Nelson, Arthur A , M D , Ph D Food and Drug Administration, Federal Security Agency, Washington, D C *Senior Pathologist, Division of Pharmacology* (4, 1942)
- Nelson, Carl Ferdinand, M D , Ph D Department of Biochemistry, University of Kansas, Lawrence *Professor of Physiological Chemistry* (2, 1914)
- Nelson, Carl T , A B , M A , M D College of Physicians and Surgeons, 630 West 168th St , New York 32, N Y *Instructor in Dermatology* (6, 1943)
- Nelson, Erwin E , Ph D , M D Drug Division, Food & Drug Administration, F S A Washington 25, D C (1, 1923, 3, 1921)
- Nelson, E M , M S , Ph D Food and Drug Administration, Federal Security Agency, Washington 25, D C *Chief, Vitamin Division* (2, 1927, 5, 1933)
- Nelson, John B , Ph D Rockefeller Institute for Medical Research, Princeton, N J *Associate Member* (4, 1934)
- Nelson, John M , Ph D Columbia University, New York City *Professor of Organic Chemistry* (2, 1923)
- Nelson, Norton, Ph D New York University College of Medicine, 477 First Ave , New York 16, N Y *Associate Professor of Industrial Medicine* (2, 1946)
- Nelson, P Mabel, M S , Ph D Iowa State College, Ames *Dean, Division of Home Economics* (5, 1934)
- Nelson, Tell, M A , M D Kula Sanitarium, Wailua, Maui, Hawaii, T H (6, 1938)
- Nelson, Victor E , M S Iowa State College, Ames *Professor of Physiological Chemistry* (2, 1924)
- Nelson, Warren O , M S , Ph D Dept of Anatomy, School of Medicine, Univ of Iowa, Iowa City *Professor of Anatomy* (1, 1937)
- Neter, Erwin, M D Children's Hospital, 219 Bryant St , Buffalo, N Y *Attending Bacteriologist* (6, 1937)
- Nettleship, Anderson, M D University of Arkansas School of Medicine, Little Rock *Professor and Head of Department of Pathology* (1, 1942)
- Neuberg, Carl, Ph D , M D (h c ), Med Chem D (h c ), Biol D (h c ), Dr Eng (h c ), LL D 536 W 113th St , New York 25, N Y *Research Professor, New York University, Member or hon member of the Academies of Science of Copenhagen, Göttingen, Leningrad, Lisbon, Lund, Prag, Rome and Upsala* (2, 1944)
- Neumann, Charles, M D 525 East 68th Street, New York 21, N Y *Resident Surgeon, New York Hospital, Instructor in Surgery, Cornell University Medical College* (1, 1911)
- Neurath, Hans, Ph D School of Medicine, Duke University, Durham, N C *Professor of Physical Biochemistry* (2, 1910, 6, 1911)
- Neuwelt, Frank, M D 501 Broadway, Gary Ind *Research Associate, Department of Gastrointestinal Research, Michael Reese Hospital* (1, 1910)
- Neuwirth, Isaac, Ph D 209 E 23rd St , New York 10, N Y *Associate Professor of Pharmacology and Therapeutics, New York University College of Dentistry* (2, 1921, 3, 1931)
- Nice, Leonard B , Ph D Chicago Medical School, 710 S Wolcott Ave , Chicago, Ill *Professor of Physiology and Pharmacology* (1, 1921)
- Nicholas, John S , M S , Ph D Osborn Zoological Laboratory, Yale University, New Haven, Conn *Bronson Professor of Comparative Anatomy* (1, 1927)
- Nicholson, Hayden C , M S , M D Division of Medical Sciences, National Research Council, 2101 Constitution Ave , Washington 25, D C (1, 1932)
- Nickerson, John L , Ph D Columbia University, 630 W 168th St , New York 32, N Y *Associate Professor of Physiology* (1, 1915)
- Nickerson, Mark, Sc M , Ph D University of Utah School of Medicine, Salt Lake City, Utah *Assistant Professor of Pharmacology* (3, 1947)
- Nicolet, Ben H , Ph D Bureau of Dairy Industry, U S Department of Agriculture, Beltsville, Md *Senior Chemist* (2, 1932)
- Nicoll, Paul A , Ph D Indiana University, Bloomington *Assistant Professor of Physiology* (1, 1945)
- Niemann, Carl G , Ph D California Institute of Technology, Pasadena 4, Calif *Professor, Organic Chemistry* (2, 1940)
- Nigg, Clara, M A , Ph D c/o E R Squibb & Sons, New Brunswick, N J (6, 1929)
- Nims, Leslie F , M A , Ph D Biology Department, Brookhaven National Laboratory, Upton, Long Island, N Y *Acting Head of Department* (1, 1910)
- Noble, Robert Laing, M D , Ph D D Sc Department of Medical Research, University of Western Ontario, London, Ontario (1, 1941)
- Nord, F F , Ph D Fordham University, Dept of Organic Chemistry, New York City *Professor of Chemistry* (2, 1940)
- Norris, Earl R , Ph D University of Washington, Seattle *Professor of Chemistry and Executive Officer* (2, 1938)
- Norris, L C , Ph D Rice Hall, Cornell Univer-



- sity, Ithaca, N Y Professor of Nutrition, Secretary, School of Nutrition (2, 1939, 5, 1931)
- Northrop, J H, M A, Ph D, Sc D, LL D Rockefeller Institute for Medical Research, Princeton, N J Member (2, 1938)
- Northup, David W, M A, Ph D West Virginia University Medical School, Morgantown Associate Professor of Physiology (1, 1936)
- Novy, F G, M D, Sc D, LL D 721 Forest Ave, Ann Arbor, Mich Dean Emeritus of the Medical School and Professor Emeritus of Bacteriology, University of Michigan, Member, National Academy of Sciences (2, 1906)
- Nye, Robert N, M D S Penury, Boston 18, Mass, Managing Editor, New England Journal of Medicine (6, 1923)
- Oberst, Fred W, M S, Ph D 3601 Victory Park way, Cincinnati 29, O Assistant Director of Research, The Murray Foundation, Inc (2, 1936)
- Ochoa, Severo, M D New York University College of Medicine, 477 First Ave, New York City 16 Professor of Pharmacology (2, 1912)
- Ogden, Eric, M R C S (England), L R C P (London) University of Texas School of Medicine, Galveston Professor of Physiology and Clinical Physiologist, John Sealy Hospital (1, 1941)
- O'Hare, James P, M D 520 Commonwealth Ave, Boston, Mass Physician, Peter Bent Brigham Hospital, Assistant Professor of Medicine, Harvard Medical School (4, 1927)
- Ohlson, Margaret A, M S, Ph D Dept of Foods and Nutrition, Michigan State College, East Lansing Professor and Head, Department of Foods and Nutrition (5, 1945)
- Okey, Ruth, Ph D 1533 Life Sciences Bldg, University of California, Berkeley Professor of Home Economics and Biochemist, State Exp Station (2, 1922, 5, 1933)
- Olcott, Harold S, M S, Ph D Western Regional Research Laboratory, U S Department of Agriculture, Albany 6, Calif Senior Chemist (2, 1935)
- Oldham, Helen, M S, Ph D University of Chicago, Chicago, Ill Assistant Professor, Dept of Home Economics (5, 1946)
- Olitsky, Peter K, M D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City Member (4, 1923, 6, 1917)
- Oliver, Jean Redman, M D Hoagland Laboratory, 335 Henry St, Brooklyn, N Y Professor of Pathology, Long Island College of Medicine (1, 1924, 4, 1924)
- Oliver, Wade W, M D Hoagland Laboratory, 335 Henry St, Brooklyn, N Y Professor of Bacteriology, Long Island College of Medicine (4 1925)
- Olmsted, J M D, M A, Ph D University of California, Berkeley Professor of Physiology (1, 1920)
- Olson, Carl, Jr, D V M, Ph D Univ of Nebraska, Lincoln, Nebr Chairman, Dept of Animal Pathology and Hygiene (4, 1937)
- Opdyke, David F, Ph D Western Reserve Medical School, Cleveland 6, O Assistant Professor of Physiology (1, 1945)
- Opie, Eugene L, M D, Sc D, LL D Rockefeller Institute for Medical Research, 66th St and York Ave, New York 21, N Y Member, National Academy of Sciences (1, 1906, 4, 1913, 6, 1923)
- Oppenheimer, Enid Tribe 121 E 61st St, New York City Instructor in Physiology, Columbia University (1, 1932)
- Oppenheimer, Ernst, M D Ciba Pharmaceutical Products, Inc, Lafayette Park, Summit, N J Vice President in charge of Medical Research (3, 1941)
- Oppenheimer, Morton Joseph, Ed M, M D 3100 N Broad St, Philadelphia, Pa Professor of Physiology, Temple University School of Medicine (1, 1912)
- Orent-Keiles, Elsa, D Sc Bureau of Human Nutrition and Home Economics, U S Department of Agriculture, Beltsville, Md In Charge of Nutrition Investigations, Assistant Chief, Foods and Nutrition Division (2, 1935, 5, 1935)
- Ort, John M, Ph D 401 Codwise Ave, New Brunswick, N J Director of Research, Carroll Dunham Smith Pharmacal Co (2, 1932)
- Orten, Aline Underhill, M S Ph D Wayne Univ College of Medicine, Detroit 26, Mich Research Associate, Dept of Physiological Chemistry (5, 1946)
- Orten, James M, M S Ph D Wayne University College of Medicine, Detroit Mich Associate Professor of Physiological Chemistry (2, 1936, 5, 1937)
- Orth, O Sidney, M S, Ph D, M D University of Wisconsin Medical School, Madison Associate Professor of Pharmacology (1, 1942, 3, 1944)
- Osborne, Stafford L, B P E, M S, Ph D Northwestern University Medical School, 303 E Chicago Ave, Chicago, Ill Associate Professor of Physical Therapy (1, 1941)
- Oser, Bernard L, M S, Ph D Food Research Laboratories, Inc, 48 14 Thirty third St, Long Island City 1, N Y Director (5, 1945)
- Oster, Robert H, Ph D University of Maryland Medical School, Greene and Lombard Sts, Baltimore Assistant Professor of Physiology. (1, 1938)
- Osterberg, Arnold E, M S, Ph D Medical Dept. Abbott Laboratories, No Chicago, Ill Associate in Medical Dept (2, 1933)
- Osterhout, Marian I Rockefeller Institute for Medical Research, 66th St and York Ave, New

- York City 21 *Associate, Division of General Physiology* (1, 1927)
- Osterhout, W J V, Ph D Rockefeller Institute, 66th St and York Ave, New York City *Member Emeritus of the Institute, Member of the National Academy of Sciences* (1, 1910)
- Otis, Arthur B, A B, Sc M, Ph D Dept of Physiology, Univ of Rochester, Rochester 7, N Y *Associate in Physiology* (1, 1946)
- Overman, Richard R, B A, M A, Ph D Dept of Physiology, Univ of Tennessee, Memphis, Tenn *Assistant Professor* (1, 1946)
- Owen, Seward E, M S, Ph D 418 So 20th Ave, Maywood, Ill *Major, S E Sn Corps* (1, 1938)
- Pace, Donald M, Ph D Dept of Physiology and Pharmacology, College of Pharmacy, University of Nebraska, Lincoln *Associate Professor of Physiology* (1, 1944)
- Pace, Nello, Ph D Division of Medical Physics, Donner Laboratory, University of California, Berkeley 4 *Research Associate* (1, 1947)
- Pack, George T, M D 139 E 36th St, New York City 16 *Fellow in Cancer Research, Memorial Hospital* (1, 1924)
- Packhamian, Ardzoony, Ph D School of Medicine, University of Texas, Galveston *Associate Professor of Bacteriology and Tropical Medicine, and Director of Laboratory of Microbiology* (6, 1943)
- Page, Edouard, Ph D Department of Biochemistry, Medical School, Laval University, Quebec, P Q, Canada (1, 1947)
- Page, Ernest W, M D Department of Obstetrics and Gynecology, University of California Hospital, San Francisco 22 *Assistant Professor* (1, 1947)
- Page, Irvine H, M D Cleveland Clinic Foundation, Euclid Ave and 93rd St, Cleveland 6, O *Director of Research* (1, 1937, 2, 1932)
- Painter, Elizabeth E, Ph D University of Illinois School of Medicine, 1853 W Polk St, Chicago *Assistant Professor of Physiology* (1, 1941)
- P'An, S Y, M D Peiping Union Medical College, Peiping, China *Assistant in Pharmacology* (3, 1941)
- Pangborn, Mary C, Ph D New Scotland Ave, Albany, N Y *Senior Biochemist, New York State Department of Health, Division of Laboratories and Research* (2, 1941)
- Pappenheimer, Alwin M, Jr, Ph D New York Univ College of Medicine, 477 First Ave, New York 16, N Y *Associate Professor of Bacteriology* (2, 1941, 6, 1938)
- Pappenheimer, Alwin M, M D 5 Acacia St, Cambridge, Mass *Professor Emeritus of Pathology, Columbia University* (4, 1922)
- Pappenheimer, John R, B S, Ph D Harvard Medical School, Boston, Mass *Associate in Physiology* (1, 1946)
- Park, Edwards A, M D Johns Hopkins Hospital, Baltimore, Md *Emeritus Professor of Pediatrics, Johns Hopkins University* (4, 1923)
- Parker, George Howard, Sc D 16 Berkeley St, Cambridge, Mass *Professor of Zoology Emeritus, Harvard University, Member of the National Academy of Sciences* (1, 1900)
- Parker, Robert F, M D Lakeside Hospital, 2065 Adelbert Rd, Cleveland, O *Associate Professor of Medicine* (4, 1942, 6, 1935)
- Parkins, William M, M A, Ph D School of Medicine, University of Pennsylvania, Philadelphia *Research Associate, Harrison Department of Surgical Research* (1, 1939)
- Parpart, Arthur K, Ph D Guyot Hall, Princeton University, Princeton, N J *Professor of Physiology* (1, 1937)
- Parr, Leland W, Ph D The George Washington University School of Medicine, 1335 H St, N W Washington, D C *Professor of Bacteriology* (4, 1940)
- Parsons, Helen T, M D, Ph D University of Wisconsin, Madison *Professor of Home Economics, In Charge of Purnell Research in Nutrition* (2, 1929, 5, 1933)
- Parsons, Robert J, M D Highland Alameda County Institution, 2701 14th Ave, Oakland, Calif *Pathologist and Director of Laboratories* (4, 1939)
- Paschkis, Karl E, M D 1025 Walnut St, Philadelphia, Pa *Assistant Professor of Medicine, Associate in Physiology, Jefferson Medical College, Chief of Endocrine Clinic, Jefferson Hospital* (1, 1942)
- Patterson, Thos L, A M, M S, Ph D, Sc D (hon) Wayne University College of Medicine, 1512 St Antoine St, Detroit, Mich *Research Professor of Physiology* (1, 1920)
- Patton, H D, Ph D, M D Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle 5 *Assistant Professor* (1, 1947)
- Paul, John R, M D, A M 330 Cedar St, New Haven, Conn *Professor of Preventive Medicine, Yale University Medical School* (4, 1927, 6, 1937)
- Pearce, John Musser, M D Long Island College of Medicine, Hoagland Laboratory, 335 Henry St, Brooklyn, N Y *Associate Professor of Pathology* (4, 1942)
- Pearce, Louise, M D Rockefeller Institute for Medical Research, Princeton, N J *Associate Member in Pathology and Bacteriology* (3, 1915, 4, 1925)
- Pearcy, Frank, Ph D, M D 2606 Oak Lawn Ave, Dallas, Texas (1, 1928)
- Pearlman, William Henry, Ph D Jefferson Medi-

- cal College, 1025 Walnut St., Philadelphia 17, Pa  
Assistant Professor, Biochemistry Department  
(2, 1946)
- Pearse, Herman D., M.D. School of Medicine  
and Dentistry, University of Rochester, Crit-  
tenden Blvd., Rochester, N. Y. Associate  
Professor of Surgery (1, 1932)
- Pearson, Paul B., Ph.D. A & M College of Texas,  
College Station. Head of Department of Bio-  
chemistry and Nutrition (2, 1944, 5, 1946)
- Pease, Marshall C., Jr., M.D. Branchville Rd.,  
R.F.D. 4, Ridgefield, Conn. (6, 1920)
- Peck, Robert L., Ph.D. 939 Madison Avenue,  
Plainfield, N. J. Senior Chemist, Merck and  
Co., Inc. (2, 1947)
- Pemberton, Ralph, M.S., M.D. University of  
Pennsylvania, Philadelphia. Professor of Medi-  
cine, Graduate School of Medicine (5, 1933)
- Penfield, Wilder G., M.D., D.Sc. McGill Uni-  
versity, Montreal, Que., Canada. Professor of  
Neurology and Neurosurgery (1, 1932)
- Pennington, Mary Engle, Ph.D. 233 Broadway,  
New York 7, N. Y. Consultant in Connection  
with the Handling, Transportation and Storage  
of Perishables (2, 1908)
- Penrod, Kenneth E., B.S., Ph.D. Boston Univ.  
School of Medicine, Dept. of Physiology, 80 E.  
Concord St., Boston, Mass. Assistant Professor  
of Physiology (1, 1946)
- Peoples, S. Anderson, M.D. Baylor University  
College of Medicine, Houston, Texas. Professor  
of Pharmacology (3, 1937)
- Pertman, Ely, A.B., M.D. Mt. Sinai Hospital,  
100th St. and Fifth Ave., New York 29, N. Y.  
Research Fellow (6, 1944)
- Perlzweig, William A., A.M., Ph.D. Box 3711,  
Duke Hospital, Durham, N. C. Professor of  
Biochemistry, Duke University, Biochemist,  
Duke Hospital (2, 1924, 5, 1944)
- Permar, Howard H., M.D. Pathologic Labora-  
tories, Mercy Hospital, Pittsburgh, Pa. Direc-  
tor of Laboratories (4, 1925)
- Petermann, Mary Locke, Ph.D. Sloan Kettering  
Institute, 414 East 68th Street, New York 21, N. Y.  
Research Fellow (2, 1947)
- Peters, John P., M.D. 123 Marvel Road, New  
Haven 15, Conn. Sterling Professor of Medicine,  
Yale University (2, 1922)
- Peters, Lawrence, B.S., Ph.D. Dept. of Pharma-  
cology, Western Reserve Univ. Medical School  
2109 Adelbert Rd., Cleveland 6, Ohio. Senior In-  
structor in Pharmacology (3, 1946)
- Petersen, William E., M.S., Ph.D. Division of  
Dairy Husbandry, University of Minnesota, St.  
Paul 1 Professor (1, 1947)
- Petersen, William F., M.D. 1322 Astor St.,  
Chicago, Ill. Director, Clinical Research, St.  
Luke's Hospital (3, 1923, 4, 1923)
- Peterson, William H., A.M., Ph.D. Biochemistry  
Building, University of Wisconsin, Madison  
Professor of Biochemistry (2, 1919, 5, 1936)
- Petroff, S. A., Ph.D., Sc.D. Sea View Hospital,  
West New Brighton, Staten Island, N. Y.  
Director of Bacteriology and Immunology  
(6, 1926)
- Pett, L. B., M.D., Ph.D. Department of National  
Health and Welfare, Ottawa, Canada. Director  
of Nutrition (2, 1937, 5, 1945)
- Peugnet, Hubert B., M.D. Department of Sur-  
gery, University of Chicago, Chicago, Ill. (1,  
1938)
- Pfeiffer, Carl C., Ph.D., M.D. Department of  
Pharmacology, University of Illinois, 1853 West  
Polk St., Chicago 12. Professor of Pharmacol-  
ogy and Chairman of Dept. (3, 1938)
- Pfiffner, Joseph J., Ph.D. Research Laboratories,  
Parke, Davis & Co., Detroit 32, Mich. Research  
Chemist (1, 1931, 2, 1931, 5, 1946)
- Phatak, Nilkanth M., M.S., Ph.D. North Pacific  
College of Oregon, School of Dentistry, Portland.  
Associate Professor of Physiology, Pharmacology,  
and Research and Instructor Dept. of Phar-  
macology, University of Oregon Medical School,  
Portland. Captain, Sn. C. (3, 1941)
- Philips, Frederick S., Ph.D. Sloan Kettering  
Institute, 414 East 68th Street, New York, N. Y.  
Chief, Pharmacology Department (3, 1947)
- Phillips, Paul H., Ph.D. University of Wisconsin,  
Madison. Professor of Biochemistry (2, 1940,  
5, 1938)
- Phillips, Robert Allan, M.D. CNO(Op. 32) Mail  
Dispatch Section, Navy Department, Washing-  
ton 25, D. C. (1, 1938)
- Pick, Ernst Peter, M.D. 19 E. 98th St., New York  
City. Associate Pharmacologist to the Mt.  
Sinai Hospital, Clinical Professor of Pharma-  
cology in Columbia University (3, 1940)
- Pierce, Harold B., M.S., Ph.D. College of Medi-  
cine, University of Vermont, Burlington. Pro-  
fessor and Chairman, Dept. of Biochemistry  
(2, 1929, 5, 1933)
- Pierce, Harold Fisher, Ph.D., M.D. 156 Ray-  
mond Rd., West Hartford 7, Conn. (1, 1928)
- Pierce, Ira H., M.S., Ph.D. Univ. of Iowa, Iowa  
City. Associate Professor of Pharmacology  
(3, 1933)
- Pike, Frank H., Ph.D. 437 W. 59th St., New  
York City 19. Associate Professor of Physi-  
ology, Columbia University (1, 1907)
- Pilcher, J. Douglas, M.D. City Hospital, Scrant-  
on Road, Cleveland, O. Associate Professor of  
Pediatrics, Western Reserve Medical School  
(3, 1911)
- Pillemer, Louis, Ph.D. Inst. of Pathology, West-  
ern Reserve Univ., Cleveland, O. (6, 1942)
- Pincus, Gregory, M.S., Sc.D. Worcester Founda-  
tion for Experimental Biology, 222 Maple Ave.,  
Shrewsbury, Mass. (1, 1935)

- Pinkerton, Henry, M D** St Louis University School of Medicine, St Louis, Mo *Professor of Pathology* (4, 1931)
- Pinkston, James O, Ph D** American University of Beirut, Beirut, Lebanon, *Professor of Physiology and Dean of Medical Faculty* (1, 1936, 3, 1939)
- Pinson, Ernest A, Ph D** AC Donner Radiation Laboratory, University of California, Berkeley *Major, Air Corps* (1, 1943)
- Pittman, Martha S, A M, Ph D** Manhattan, Kansas (5, 1933)
- Pitts, Robert F, Ph D, M D** Syracuse Univ College of Medicine, Syracuse, N Y *Professor of Physiology and Head of the Department of Physiology* (1, 1934)
- Plass, Everett D, M D** University Hospital, Iowa City, Iowa *Professor and Head of Department of Obstetrics and Gynecology, State University of Iowa* (2, 1922)
- Pohlman, Augustus G, M D** 4056 Farmouth Dr, Los Angeles, Calif *Associate Clinical Professor, Department of Otolaryngology, University of Southern California School of Medicine* (1, 1934)
- Pollack, Herbert, Ph D, M D** 15 E 66th St, New York City 21 *Associate Physician and Chief of Metabolism Clinics, Mt Sinai Hospital* (1, 1933, 5, 1935)
- Pomerat, Charles Marc, Ph D** University of Texas Medical School, Galveston *Professor of Anatomy* (1, 1944)
- Pommerenke, W T, A M, Ph D, M D** University of Rochester School of Medicine and Dentistry, Rochester 7, N Y *Associate Professor of Obstetrics and Gynecology* (1, 1947)
- Pond, Samuel E, A M, Ph D** 400 S Main St, East Hartford, Conn *Consulting Engineer, P and W A Division, United Aircraft Corp* (1, 1924)
- Ponder, Eric, M D, Sc D** The Nassau Hospital, Mineola, Long Island, N Y (1, 1931)
- Popper, Hans, Ph D, M D** Cook County Hospital, 1825 W Harrison St, Chicago 12, Ill *Director of Department of Pathology and Research Director of Hektoen Institute for Medical Research, Assistant Professor of Pathology, Northwestern University Medical School* (4, 1942)
- Porter, Eugene L, A M, Ph D** University of Texas, Medical Branch, Galveston *Professor of Physiology* (1, 1913)
- Porter, Thelma, Ph D** University of Chicago, Chicago, Ill *Prof and Head of Department of Home Economics* (5, 1944)
- Porter, William Townsend, M D, Sc D, LL D** Dover, Mass *Professor Emeritus of Comparative Physiology, Harvard University* (1, 1891)
- Poth, Edgar J, M D, M A, Ph D** Univ of Texas Med School, Galveston, Texas *Professor of Surgery* (1, 1946)
- Potter, Truman S, M D** 82 N Prospect St, Amherst, Mass (6, 1939)
- Potter, Van Rensselaer, M S, Ph D** McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison *Professor of Oncology* (2, 1941)
- Povitzky, Olga R, M D, D P H** 235 E 22nd St, New York City *Bacteriologist, Bureau of Laboratories, New York City Department of Health* (6, 1920)
- Powell, Horace M, Sc D** 5565 Washington Blvd, Indianapolis, Ind *Bacteriologist, Eli Lilly & Co* (6, 1934)
- Power, Marschelle H, M S, Ph D** Mayo Clinic, Rochester, Minn *Associate Professor of Physiological Chemistry, Mayo Foundation, University of Minnesota* (2, 1932)
- Pratt, Frederick H, A M, M D** Wellesley Hills 82, Mass *Professor of Physiology, Emeritus, Boston University School of Medicine* (1, 1919)
- Pratt, Joseph H, A M, M D Sc D** New England Medical Center, 25 Bennet St, Boston, Mass *Physician-in-Chief, Boston Dispensary, and Joseph H Pratt Diagnostic Clinic, Professor of Clinical Medicine, Tufts Medical School* (1, 1910, 3, 1910, 1, 1927)
- Preisler, Paul W, M S, Ph D** 1580 Scott Ave, St Louis 10, Mo *Assistant Professor of Biochemistry, Washington University Medical School* (2, 1931)
- Prinzmetal, Myron, M A, M D** 2007 Wilshire Blvd, Los Angeles, Calif *Instructor in Medicine and Lecturer in Physiology, University of Southern California Medical School* (3, 1941)
- Prosser, C Ladd, Ph D** Natural History Building, University of Illinois, Urbana (1, 1935)
- Puestow, Charles B, M D, M S, Ph D** University of Illinois, College of Medicine, 1853 W Polk St, Chicago *Assistant Professor of Surgery* (1, 1934)
- Pugsley, Leonard I, M Sc, Ph D** Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, Canada *Pharmacologist* (2, 1937)
- Putnam, Frank W, M A, Ph D** Abbott Hall, 947 East 58th Street, Chicago 37, Ill *Research Associate and Assistant Professor, Department of Biochemistry, University of Chicago* (2, 1947)
- Quackenbush, Forrest W, Ph D** 243 Connolly St, W Lafayette, Ind *Professor and Head of Dept of Agricultural Chemistry, Purdue Univ* (2, 1946)
- Queen, Frank B, M D** Univ of Oregon School of Medicine, 3181 S W Marquam Hill Rd, Portland, Oregon (4, 1941)

- Quick, Armand J, M D, Ph D 561 N 15th St, Milwaukee 3, Wis *Professor of Biochemistry, Marquette Medical School Milwaukee* (2, 1932, 3, 1937)
- Quigley, J P, M S, Ph D Division of Physiology and Pharmacology, Univ of Tenn, Memphis 3, Tenn *Professor and Chief of the Division* (1, 1929, 3, 1945)
- Quinby, William Carter, M D Peter Bent Brigham Hospital, Boston, Mass *Clinical Professor of Genito urinary Surgery, Harvard Medical School* (1, 1916)
- Quinn, Edmond John, Ph D 106 N Lee Ave, Rockville Center, Long Island, N Y *Medical Sales Division, Merck & Co, Inc, Rahway, N J* (2, 1927, 5, 1933)
- Rabinowitch, I M, O B I, D Sc, M D, C M, F R C P, F A C P 1020 Medical Arts Bldg, Sherbrooke and Guy Sts, Montreal 25, Canada *Associate Professor of Medicine and Lecturer in Biochemistry, McGill University, Director, Department of Metabolism, Montreal General Hospital* (2, 1928, 5, 1933)
- Rackemann, Francis M, M D 263 Beacon St, Boston, Mass *Physician, Massachusetts General Hospital, Lecturer in Medicine, Harvard Medical School* (6, 1923)
- Raffel, Sidney, Sc D, M D Department of Bacteriology and Experimental Pathology, Stanford University, Calif *Assistant Professor* (6, 1938)
- Rahn, Hermann, Ph D University of Rochester School of Medicine and Dentistry, Rochester, N Y *Assistant Professor of Physiology* (1, 1944)
- Rake, Geoffrey W, M B, M R C S, L R C P Division of Microbiology, The Squibb Institute for Medical Research, New Brunswick, N J *Head, Division of Microbiology* (6, 1939)
- Rakestraw, Norris W Ph D Scripps Institution of Oceanography University of California, LaJolla *Professor of Chemistry* (2 1925)
- Rakieten, Nathan, Ph D Bristol Laboratories, Inc, P O Box 657 Syracuse 2, N Y *Pharmacologist and Toxicologist* (1 1941)
- Ralli, Elaine P, M D 477 First Ave, New York City *Associate Professor of Medicine, New York University College of Medicine* (1, 1931, 5, 1933)
- Ralston, H J, Ph D Department of Physiology, College of Physicians and Surgeons, 344 14th St, San Francisco 3, Calif *Assistant Professor of Physiology* (1, 1947)
- Rammelkamp, Charles H, Jr, B A, M D Dept of Preventive Medicine, Western Reserve Univ, Cleveland 6, Ohio *Assistant Professor of Medicine* (6, 1943)
- Ramsey, Robert Weberg, M S, P *Medical College of Virginia, Richmond*
- essor of Physiology and Pharmacology* (1, 1939)
- Randall, Lowell O, Ph D Hoffmann LaRoche, Inc, Nutley 10, N J *Pharmacologist* (2, 1939)
- Randall, Walter C, M S, Ph D St Louis University, School of Medicine, 1402 S Grand Blvd, St Louis, Mo *Instructor in Physiology* (1, 1943)
- Randall, William A, B S, M S, Ph D Food and Drug Administration, Washington 25, D C *Bacteriologist, Division of Penicillin Control and Immunology* (6, 1946)
- Rane, Leo, Ph D Lederle Laboratories, Inc, Pearl River, N Y *Department Head, Normal Blood Plasma* (6, 1942)
- Rantz, Lowell A, A B, M D Stanford Univ Hospital, San Francisco 15, Calif *Assistant Professor of Medicine* (3, 1916)
- Rapaport, Samuel, M D, Ph D The Children's Hospital Research Foundation, Elland and Bethesda, Cincinnati, O *Research Associate* (2, 1941)
- Rapport, David, M D 416 Huntington Ave, Boston, Mass *Professor of Physiology, Tufts College Medical School* (1, 1922)
- Raska, Sigwin, Ph D, M A Barnes Hospital, St Louis, Mo (1, 1947)
- Rasmussen, Andrew Theodore, Ph D University of Minnesota Medical School, Minneapolis *Professor of Neurology* (1, 1919)
- Ratner, Bret, M D 50 E 78th St, New York City *Professor of Pediatrics, New York Univ College of Medicine* (4, 1940, 6, 1928)
- Ratner, Sarah, Ph D Dept of Pharmacology, N Y Univ College of Medicine, 477 First Ave, New York 16, N Y *Assistant Professor of Pharmacology* (2 1944)
- Raulston, B O A B M D 200 S Hudson Ave, Los Angeles, Calif *Professor of Medicine, Director of Clinical Teaching, and Associate Dean, the University of Southern California, School of Medicine* (3, 1942)
- Ravdin, I S, M D University of Pennsylvania School of Medicine, Philadelphia *John Rea Barton Professor of Surgery Chief Surgeon, Hospital of the University of Pennsylvania* (1, 1930, 1, 1930)
- Rawson, Rulon W, M D Massachusetts General Hospital Boston *Associate in Medicine Assistant Professor of Medicine, Harvard Medical School* (1, 1947)
- Raymond, Albert L, Ph D G D Searle & Co, P O Box 5110, Chicago 80, Ill *Vice President* (2, 1932)
- Reback, John F, B S, M S 317 E Dubuik Ave South Bend 14, Ind *Bacteriologist, 4th G Hospital, A I S* (6, 1943)
- Redfield, Alfred C, Ph D

- Professor of Physiology, Harvard University* (1, 1919)
- Reed, Carlos Isaac, A M, Ph D College of Medicine, University of Illinois, 1853 W Polk St, Chicago *Professor of Physiology* (1, 1923)
- Reed, Howard S, Ph D 3048 Life Sciences Bldg, University of California, Berkeley *Professor of Plant Physiology* (2, 1909)
- Rehm, Warren S, Jr, Ph D, M D University of Louisville School of Medicine, Louisville, Ky *Assistant Professor of Physiology* (1, 1945)
- Reid, Mary E, Ph D National Institute of Health, Bethesda 14, Md *Cytologist* (5, 1917)
- Reid, Marion Adelaide, A M, Ph D New Jersey College for Women, New Brunswick, N J (1, 1941)
- Reimann, Hobart A, M D Jefferson Hospital, Philadelphia, Pa *Professor of Medicine, Jefferson Medical College* (4, 1933)
- Reimann, Stanley P, M D, Sc D 703 W Philadelphia St, Mount Airy, Philadelphia, Pa *Director of the Research Institute of the Lankenau Hospital, Director, Institute of Cancer Research Associate Professor of Surgical Pathology, Graduate School of Medicine, University of Pennsylvania, Professor of Oncology, Hahnemann Medical College and Hospital, Philadelphia* (1, 1921, 4, 1924)
- Reinecke, Roger M, M A, M B, Ph D, M D Department of Physiology, University of Minnesota, Minneapolis 14 *Assistant Professor* (1, 1947)
- Reiner, John M, M S, Ph D Department of Bacteriology and Immunology, Washington University School of Medicine, St Louis 10, Mo *Research Fellow* (1, 1947)
- Reiner, Laszlo, M D, Ph D 165 Franklin St, Bloomfield, N J *Director, Pharmaceutical Research, Wallace & Tieman Products, Inc* (2, 1942, 6, 1933)
- Reinhold, John G, M S, Ph D Philadelphia General Hospital, 34th St and Curie Ave, Philadelphia, Pa *Principal Biochemist, Instructor in Physiological Chemistry, University of Pennsylvania* (2, 1936)
- Remington, John W, M S, Ph D University of Georgia, School of Medicine, Augusta *Assistant Professor of Physiology* (1, 1943)
- Remington, Roe E, M A, Ph D, D Sc Hendersonville, N C *Consultant* (2, 1930, 5, 1934)
- Renfrew, Alice G, Ph D Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa *Fellow, Department of Research in Pure Chemistry* (2, 1939)
- Renshaw, Birdsey, M A, Ph D University of Oregon Medical School, Portland (1, 1941)
- Reynolds, Chapman, M D Louisiana State University, School of Medicine, New Orleans *Assistant Professor of Pharmacology* (3, 1937)
- Reynolds, Samuel R M, Ph D 4028 Deepwood Rd, Baltimore 18, Md *Carnegie Institution of Washington, Dept of Embryology, Staff Member and Physiologist* (1, 1932)
- Reznikoff, Paul, M D New York Hospital, 525 E 68th St, New York City *Associate Professor of Clinical Medicine, Cornell University Medical College* (1, 1927)
- Rhoads, Cornelius Packard, M D Memorial Hospital, 414 E 68th St, New York City *Director, Professor of Pathology, Cornell University Medical College, Director of Sloan-Kettering Institute for Cancer Research* (4, 1930)
- Rhoads, Jonathan Evans, B A, M D, D Sc 4023 Pine St, Philadelphia 1, Pa *Assistant Professor of Surgical Research* (1, 1916)
- Rice, Christine E, M A Animal Diseases Research Inst, Canadian Dept of Agriculture, Hull, Quebec, Canada *Assistant Bacteriologist* (6, 1938)
- Rice, James C, A M, Ph D University of Mississippi, P O Box 475, University *Professor of Pharmacology* (3, 1941)
- Rich, Arnold Rice, M D Johns Hopkins Hospital, Baltimore, Md *Professor of Pathology, Johns Hopkins University* (4, 1924)
- Richards, Alfred N, A M, Ph D, Sc D, M D (hon), LL D University of Pennsylvania Medical School, Philadelphia *Professor of Pharmacology and Vice-President in Charge of Medical Affairs, Member, National Academy of Sciences* (1, 1900, 2, 1906, 3, 1909)
- Richards, Oscar W, M A, Ph D American Optical Co, Scientific Instrument Division, Box A Buffalo 15, N Y *Chief Biologist* (1, 1934)
- Richards, Richard Kohn, M D Abbott Laboratories, North Chicago, Ill *Director, Pharmacologic Research, Lecturer in Pharmacology, Northwestern University Medical School, Chicago* (1, 1938, 3, 1947)
- Richardson, Authur P, M D Department of Pharmacology, Emory University School of Medicine, Emory University, Ga *Professor of Pharmacology* (3, 1939)
- Richardson, Luther R, Ph D P O Box 102, College Station, Texas (5, 1942)
- Richter, Curt P, Ph D Phipps Psychiatric Clinic, The Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Psycho-biology, Johns Hopkins University* (1, 1924)
- Richter, Maurice N, M D 303 E 20th St, New York City *Professor of Pathology, Columbia University, New York Post Graduate Medical School, Director, Department of Pathology, New York Post-Graduate Medical School and Hospital, Acting Director of Bacteriology,*

- New York Post-Graduate Medical School and Hospital (4, 1931)
- Ricketts, Henry T, M D Dept of Medicine, University of Chicago, Chicago, Ill Associate Professor of Medicine (1, 1910)
- Riddle, Oscar, Ph D Cold Spring Harbor, L I, N Y Visiting Professor from the U S (in South America), Member of the National Academy of Sciences (1, 1919)
- Riegel, Byron, A M, Ph D Department of Chemistry, Northwestern University, Evanston, Ill Associate Professor (2, 1942)
- Riegel, Cecilia, M S, Ph D Room 563, University Hospital, Philadelphia, Pa Research Associate, Department of Research Surgery, University of Pennsylvania School of Medicine (2, 1938)
- Ries, Fred A, M D 139 East North Ave, Baltimore 2, Md Instructor in Neurology, Johns Hopkins University (1 1933)
- Rigdon, R H, M D Medical Branch, Univ of Texas, Galveston Professor of Experimental Pathology (4, 1941)
- Riggs, Lloyd K, Ph D % Kraft Cheese Co, 500 Peshtigo Court, Chicago, Ill Director of Research (2, 1929)
- Riker, Walter F, Jr, M D Cornell University Medical College, 1300 York Avenue, New York, 21, N Y Assistant Professor of Pharmacology (3, 1947)
- Rinehart, James F, M D University of California Medical School, Parnassus and Third Aves, San Francisco Professor of Pathology (4, 1933)
- Ring, Gordon C, M A, Ph D Temple University Medical School, Broad St, Philadelphia, Pa (1, 1933)
- Rioch, David McKenzie, M D Chestnut Lodge Sanitarium, 500 W Montgomery Ave, Rockville, Md Director of Research (1, 1931)
- Rittenberg, David, Ph D 630 W 168th St, New York City Assistant Professor, College of Physicians and Surgeons, Columbia University (2, 1939)
- Ritzman, E G, A M, Science (hon) University of New Hampshire, Durham Research Professor (5, 1933)
- Rivers, T M, M D, Sc D The Hospital of the Rockefeller Institute for Medical Research, 66th St and York Ave, New York City Director of the Hospital, Member of the National Academy of Sciences (4, 1925, 6, 1921)
- Robb, Jane Sands, Sc D, M D College of Medicine, Syracuse University, 761 Irving Ave, Syracuse, N Y Associate Professor of Pharmacology (1, 1924)
- Robbie, W A, M S, Ph D Department of Ophthalmology, College of Medicine, State University of Iowa, Iowa City Research Associate Professor of Ophthalmology and Physiology (1, 1917)
- Robbins, Benjamin Howard, M S, M D Vanderbilt Univ School of Medicine, Nashville, Tenn Associate Professor of Pharmacology (3, 1936)
- Robbins, Mary L, B A, M A, Ph D George Washington Univ School of Medicine, 1335 H Street, N W, Washington 5, D C Instructor in Bacteriology (6, 1946)
- Roberts, Edward F, M D, Ph D Wyeth, Inc 1600 Arch St, Philadelphia 3, Pa Director of Clinical Investigation (6, 1932)
- Roberts, Joseph F, M S, M D, Ph D University of Arkansas School of Medicine, Little Rock Dean (1, 1947)
- Roberts, Lydia J, Ph D University of Chicago, Chicago, Ill Professor and Chairman of Department of Home Economics (5, 1933)
- Roberts, Sidney, S B, M S, Ph D Department of Physiological Chemistry, Yale University School of Medicine, New Haven, Conn Research Assistant Professor (1, 1946)
- Robertson, Elizabeth Chant, M D, M A, Ph D University of Toronto, Toronto, Canada Research Fellow in Paediatrics (5, 1939)
- Robertson, Oswald H, M D University of Chicago, Chicago, Ill Professor of Medicine (4, 1932)
- Robinson, Charles Summers, Ph D Medical School, Vanderbilt University, Nashville, Tenn Professor of Biochemistry (2, 1925)
- Robinson, Elliott S, B A, M D, Ph D R F D #4, Laconia, N H Director, Division of Biologic Laboratories, Mass Dept of Health (Leave of Absence) (6, 1935)
- Robinson, G Canby, M D, Sc D, LL D Johns Hopkins Hospital, Baltimore, Md Lecturer in Medicine, Johns Hopkins University (1, 1912, 3, 1921)
- Robinson, Harry J, Ph D Merck Institute for Therapeutic Research, Rahway, N J Assistant Director (3, 1946)
- Robinson, Herbert E, Ph D Swift and Company, Research Laboratories, Union Stock Yards, Chicago 9, Ill Assistant Director of Research (5, 1947)
- Robinson, Howard W, M S, Ph D Broad and Ontario Sts, Philadelphia, Pa Professor of Physiological Chemistry, Temple University School of Medicine (2, 1929)
- Robinson, Sid, Ph D Indiana University Medical School, Bloomington Associate Professor of Physiology (1, 1941)
- Roblin, Richard O, Jr, M A, Ph D 1937 West Main St, Stamford, Conn Director, Chemotherapy Division, American Cyanamid Co (2, 1946, 6, 1947)
- Robscheit-Robbins, F S, Ph D University of Rochester School of Medicine and Dentistry,



- Rochester, N Y *Associate in Pathology* (1, 1925, 4, 1930)
- Rodbard, Simon, Ph D Cardiovascular Dept, Michael Reese Hospital, 29th and Ellis Aves, Chicago, Ill (1, 1942)
- Roe, Joseph Hiram, M A, Ph D George Washington University School of Medicine, Washington, D C *Professor of Biochemistry* (2, 1927, 5, 1933)
- Roeder, Kenneth D, M A Tufts College, Medford, Mass *Associate Professor of Biology* (1, 1942)
- Roepke, Martin Henry, Ph D University Farm, St Paul, Minn *Professor, Veterinary Medicine* (3, 1937)
- Rogers, Charles G, A M, Ph D, Sc D Oberlin College, Oberlin, O *Professor of Comparative Physiology* (1, 1911)
- Rogers, Fred T, A M, Ph D, M D Dallas Medical and Surgical Clinic, 4105 Live Oak St, Dallas 1, Texas (1, 1917)
- Rogoff, Julius M, Ph G, M D, Sc D School of Medicine, University of Pittsburgh, Pittsburgh, Pa *Professor of Endocrinology* (1, 1916, 3, 1916)
- Ronzoni, Ethel, M A, Ph D Washington University Medical School, St Louis 1, Mo *Assistant Professor of Biological Chemistry* (2, 1923)
- Root, Howard F, M D 14 Dwight St, Brookline, Mass *Associate in Medicine, Harvard Medical School* (5, 1933)
- Root, Walter S, Ph D College of Physicians and Surgeons, Columbia University, 630 W 168th St, New York City *Associate Professor of Physiology* (1, 1932)
- Rosahn, Paul D, M D 92 Grand St, New Britain, Conn *Pathologist, New Britain General Hospital, Associate Clinical Professor of Pathology, Yale University School of Medicine, New Haven* (4, 1934)
- Rose, Anton Richard, M S, Ph D Box 176, Edgewater, N J *Retired* (2, 1916, 5, 1933)
- Rose, William C, Ph D, D Sc University of Illinois, Urbana *Professor of Biochemistry, Member, National Academy of Sciences* (2, 1912, 5, 1933)
- Rosenblueth, Arturo, M D Instituto Nacional de Cardiologia, Calzada de la Piedad 300, Mexico D F, Mexico (1, 1932)
- Rosenfeld, Morris, M D Johns Hopkins School of Medicine, Baltimore, Md *Associate in Pharmacology and Experimental Therapeutics Captain, M C* (3, 1934)
- Rosenow, Edward C, M D, hon LL D and D Sc Research Dept, Longview State Hospital, Cincinnati 16, Ohio (4, 1913, 6, 1915)
- Rosenthal, Otto, M D 4422 Osage Ave, Philadelphia 4, Pa *Associate in Cancer Research, Harrison Dept of Surgical Research and Dept of Physiol Chem, Univ of Pennsylvania* (2, 1946)
- Rosenthal, Sanford M, M D National Institute of Health, Bethesda, Md *Senior Pharmacologist, U S Public Health Service* (3, 1925)
- Rosenthal, S R, M D, Ph D University of Illinois College of Medicine, Chicago *Assistant Professor of Bacteriology and Public Health, Director, Tice Laboratory for B C G Vaccination against Tuberculosis, Municipal Tuberculosis Sanatorium* (1, 1941)
- Ross, Joseph F, M D The Robert Dawson Evans Memorial, 65 E Newton St, Boston, Mass *Member of the Department, Physician, Massachusetts Memorial Hospital, Associate Professor of Medicine, Boston University School of Medicine* (4, 1911)
- Rostorfer, Howard Hayes, B A, M S, Ph D Department of Physiology, Indiana University, Bloomington, Indiana *Assistant Professor of Physiology* (1, 1916)
- Roth, George B, M D George Washington Univ 3811 Teak St, N W, Washington 7, D C *Emeritus Professor of Pharmacology* (1, 1914, 3, 1914)
- Roth, Grace M, M S, Ph D Mayo Clinic, Rochester, Minn *Associate in Clinical Physiology* (1, 1939)
- Roth, L W, M A, Ph D Department of Pharmacology, The Abbott Research Laboratories, North Chicago, Ill *Research Pharmacologist* (1, 1917)
- Rothmund, Paul W K, Dipl-Ing, Dr-Ing (Munich) Antioch College, Yellow Springs, O *Professor of Biochemistry, and Research Chemist, The C I Kettering Foundation, Antioch College, Associate Professor (Non resident), Department of Chemistry, Ohio State University* (2, 1940)
- Rous, Peyton, M D, Sc D Rockefeller Institute for Medical Research, York Ave at 66th St, New York City *Member, Member of the National Academy of Sciences* (4, 1913)
- Routh, Joseph I, M S, Ph D Chemistry Department, State University of Iowa, Iowa City *Associate Professor of Biochemistry* (2, 1912)
- Rovenstine, Emery Andrew, A B, M D 477 First Ave, New York, N Y *Professor of Anesthesia, New York University, Director, Division of Anesthesia, Bellevue Hospital* (3, 1914)
- Rowntree, Jennie I, M S, Ph D University of Washington, Seattle *Professor of Home Economics* (5, 1933)
- Rowntree, L G, M D, Sc D DuPont Building, Miami, Fla (1, 1911, 2, 1910, 3, 1908, 4, prior to 1920)
- Rubenstein, Boris B, Ph D, M D Dept of Metabolic & Endocrine Research, Michael Reese

- Hospital, East 59th St & Ellis Ave, Chicago, Ill (1, 1934)
- Rubin, Saul H., M.S., Ph.D. Hoffmann-La Roche, Inc., Nutley 10, N. J. *Director, Nutrition Laboratories* (2, 5, 1947)
- Ruch, Theodore C., M.A., Ph.D. 2013 Physiology Hall, University of Washington, Seattle 5 *Professor of Physiology and Biophysics* (1, 1933)
- Rusch, Harold Paul, M.D. University of Wisconsin Medical School, McArdle Memorial Laboratory, Madison 6 *Professor of Oncology Director of McArdle Memorial Laboratory for Cancer Research* (1, 1940)
- Russell, Walter C., Ph.D., Sc.D. (hon.) New Jersey Agricultural Experiment Station, Rutgers University, New Brunswick *Research Specialist and Professor of Agricultural Biochemistry* (2, 1932, 5, 1933)
- Ryan, Andrew Howard, M.D. Chicago Medical School, 710 S. Wolcott Ave., Chicago, Ill. *Associate Professor of Physiology and Pharmacology* (1, 1912)
- Rytand, David A., M.D. Stanford Univ. Hospital, San Francisco 15, Calif. *Assistant Professor of Medicine, Stanford Univ. School of Medicine* (3, 1946)
- Sabin, Albert Children's Hospital Research Foundation, Cincinnati Ohio (6, 1946)
- Sabin, Florence R., M.D., Sc.D. 1333 E. 10th Ave., Denver 3, Colo. *Member Emeritus, Rockefeller Inst., Member of National Academy of Sciences* (1, 1923)
- Sachs, Ernest, M.D. 97 Arundel Pl., St. Louis, Mo. *Professor Emeritus of Clinical Neurological Surgery, Washington University Medical School* (1, 1910)
- Sacks, Jacob, Ph.D. M.D. Biology Dept., Brookhaven National Laboratory, Upton L. I., N. Y. *Scientist* (3, 1933)
- Sah, Peter, P. T., M.S., Ph.D. Division of Pharmacology and Experimental Therapeutics, Univ. of Calif. Medical School, San Francisco, Calif. *Lecturer in Pharmacology* (3, 1941)
- Sahyun, Melville, A. M., Ph.D. Frederick Stearns & Co. Division, Sterling Drug, Inc., 6333 E. Jefferson Ave., Detroit, Mich. *Vice President and Director of Research* (2, 1932)
- Salk, Jonas E., M.D. School of Medicine University of Pittsburgh Pittsburgh, Penn. *Associate Research Professor of Bacteriology* (6, 1947)
- Salmon, W. D., A. M. Alabama Polytechnic Institute, Auburn *Animal Nutritionist* (2, 1929, 5, 1933)
- Salter, William T., B. A., M.D. Yale School of Medicine, 333 Cedar St., New Haven, Conn. *Professor of Pharmacology* (1, 1933, 3, 1942, 5, 1934)
- Samuels, Florence E., M.D. 136 E. 58th St., New York City *Physician, Allergy, O. P. D., New York Hospital* (6, 1913)
- Sampson, John J., M.D. 190 Post St., San Francisco, Calif. (1, 1932)
- Sampson, Myra M., A. M., Ph.D. Smith College, Northampton, Mass. *Professor of Zoology* (5, 1935)
- Samuels, Leo T., Ph.D. University of Utah Medical School, Salt Lake City *Professor and Head of Dept. of Biochemistry* (2, 1941, 3, 1937)
- Sandels, Margaret R., A. M., Ph.D. Florida State College for Women, Tallahassee *Dean of School of Home Economics, Professor of Nutrition* (5, 1933)
- Sandiford, Irene, Ph.D. Billings Hospital, University of Chicago, Chicago, Ill. *Assistant Professor of Medicine* (2, 1925, 5, 1933)
- Sandow, Alexander, Ph.D. Washington Square College, New York University, New York 3, N. Y. *Assistant Professor of Biology* (1, 1915)
- Sandweiss, David J., M.D. 9739 Dexter Ave., Detroit, Mich. *Instructor in Clinical Medicine, Wayne University College of Medicine, Physician, Harper Hospital (O.P.D.), Attending Physician Gastroenterology and Gastroscopy, North End Community Fund Clinic* (1, 1944)
- Sanford Arthur H., A. M., M.D. Clinical Laboratories, Mayo Clinic, Rochester, Minn. *Head, Division of Clinical Laboratories* (6, 1920)
- Santos, Francisco O., M.S., Ph.D. University of the Philippines, Los Banos, Laguna *Professor and Head of Department of Agricultural Chemistry, College of Agriculture* (5, 1936)
- Saphir, Otto, M.D. Michael Reese Hospital, 29th St and Ellis Ave., Chicago 16, Ill. *Pathologist, Michael Reese Hospital, Clinical Professor of Pathology, University of Illinois Medical School* (4, 1927)
- Sappington, Samuel W., M.D., D.Sc. P. O. Box 51, Bryn Mawr, Pa. *Professor of Pathology, Hahnemann Hospital* (6, 1913)
- Sarett, Herbert P., M.S., Ph.D. Tulane Medical School, 1430 Tulane Ave., New Orleans 13, La. *Assistant Professor of Biochemistry* (2, 1946, 5, 1947)
- Saslow, George, Ph.D., M.D. Department of Neuropsychiatry, Washington University Medical School, 640 South Kingshighway, St. Louis, Mo. *Assistant Professor of Psychiatry Associate Physician to the Student Health Service* (1, 1936)
- Satterfield, G. Howard, A. M. State College of Agriculture and Engineering, University of North Carolina, Raleigh *Professor of Biochemistry* (2, 1944, 5, 1941)
- Saul, Leon Joseph, M.A., M.D. Room 1907, 255 S. 17th St., Philadelphia 3, Pa. (1, 1933)

- Saunders, Felix, Ph D 231 Playa del Sur, La Jolla, Calif (2, 1938)
- Sawyer, Margaret E MacKay, M A , Ph D 142 Lower Albert St , Kingston, Ontario, Canada (1, 1935)
- Sawyer, Wilbur A , M D 3927 Idaho Ave , N W , Washington, D C (4, 1930, 6, 1935)
- Saxton, John A , Jr , M D Snodgrass Laboratory of Pathology and Bacteriology, 1426 Carroll St , St Louis, Mo Assistant Professor of Pathology, Washington University School of Medicine, Medical Director, Pathology, Hospital Division, City of St Louis (4, 1944)
- Sayers, George, M S , Ph D Department of Pharmacology, University of Utah, Salt Lake City 1, Utah Assistant Professor of Pharmacology (3, 1947)
- Scammon, Richard E , M A , Ph D 172 S E Bedford St , Minneapolis, Minn Distinguished Service Professor in the Graduate School, University of Minnesota (1, 1923)
- Schales, Otto, D Sc Ochsner Clinic, Prytania and Aline Sts , New Orleans, La Director of Chemical Research, Ochsner Foundation, Director of the Biochemical Laboratory, Ochsner Clinic, Assistant Professor of Biochemistry, Tulane University School of Medicine (2, 1944)
- Scharles, Frederick H , M D 213 E Franklin, Silver Spring, Md (5, 1935)
- Schattenberg, Herbert John, M S , M D Laboratory of Clinical Pathology, 220-222 Medical Arts Bldg , San Antonio, Texas Director (4, 1940)
- Schenken, John R , M D Univ of Nebraska College of Medicine, Omaha, Neb Professor of Pathology and Bacteriology (4, 1942)
- Scherp, Henry W , M S , Ph D Univ of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd , Rochester 7, N Y Associate Professor of Bacteriology and Immunology (6, 1940)
- Schick, Bela, M D 17 E 84th St , New York City Pediatrician, Mt Sinai Hospital, Sea View Hospital (6, 1924)
- Schiffman, Milton J , M S , Ph D Hoffmann-LaRoche, Inc 919 N Michigan Ave , Chicago 11, Ill Research Consultant (1, 1943)
- Schlenk, Fritz, Ph D Science Hall, Iowa State College, Ames Professor of Bacteriology (2, 1942)
- Schlesinger, M J , Ph D , M D Beth Israel Hospital, 330 Brookline Ave , Boston, Mass Assistant Professor of Pathology, Harvard Medical School, Director of Pathology, Beth Israel Hospital (4, 1942, 6, 1921)
- Schlomovitz, Benjamin H , M D 1210 Majestic Bldg , 231 W Wisconsin Ave , Milwaukee, Wis Director, Clinical and Research Laboratory, Veterans Administration Hospital, Wood, Wisconsin (1, 1919)
- Schlumberger, Hans G , M D Ohio State University School of Medicine, Columbus Associate Professor in Pathology (4, 1945)
- Schmeisser, Harry C , M D University of Tennessee, Memphis Professor of Pathology (4, 1937)
- Schmidt, Carl F , M D Medical School, University of Pennsylvania, Philadelphia Professor of Pharmacology (1, 1929, 3, 1924)
- Schmidt, C Robert, Ph D , M D Hertzler Clinic, Halstead, Kan Resident Surgeon Major (MC) A U S (1, 1940)
- Schmidt, Gerhard, M D Boston Dispensary, 25 Bennett St , Boston, Mass Senior Research Fellow, Tufts College Medical School (2, 1939)
- Schmidt, Leon H , M S , Ph D Christ Hospital, Institute for Medical Research, Cincinnati, O Director of Research, Associate Research Professor of Biochemistry, College of Medicine, University of Cincinnati (2, 1936, 3, 1946)
- Schmitt, Francis Otto, Ph D Dept of Biology, Massachusetts Institute of Technology, Cambridge Professor of Biology (1, 1930)
- Schmitt, Otto H , Ph D Department of Physics, University of Minnesota, Minneapolis 14 Associate Professor of Zoology and Physics (1, 1947)
- Schnedorf, Jerome G , M D , Ph D 3111 Argonne Circle, Santa Barbara, Calif (1, 1941)
- Schneider, Edward C , Ph D , Sc D , M P E 25 Gordon Place, Middletown, Conn Professor Emeritus of Biology, Wesleyan University (1, 1912, 2, 1912)
- Schneider, Howard A , M S , Ph D The Rockefeller Institute for Medical Research, 66th Street and York Avenue, New York 21, N Y Associate (5, 1917)
- Schneerson, S Stanley, M D Mount Sinai Hospital, 2 East 100th St , New York 29, N Y Associate Bacteriologist (6, 1946)
- Schoenbach, Emanuel B , M D Johns Hopkins School of Hygiene, 615 N Wolfe St , Baltimore, Md Associate Professor of Preventive Medicine (6, 1941)
- Schoepfle, Gordon M , A M , Ph D Washington University, School of Medicine, St Louis, Mo Assistant Professor of Physiology (1, 1943)
- Scholander, P F , M D , Ph D Department of Zoology, Swarthmore College, Swarthmore, Pa Research Biologist (1, 1947)
- Schradieck, Constant E , M D 825 Chalkstone Ave , Providence, R I Director, Pathological Department, Homeopathic Hospital of Rhode Island (6, 1921)
- Schreiner, Oswald, M S , Ph D Bureau of Plant Industry, U S Department of Agriculture,

- Washington 25, D C Chief, Division of Soil Fertility Investigations (2, 1908)
- Schroeder, E F, M S, Ph D G D Searle & Co, P O Box 5110, Chicago 90, Ill Research Biochemist (2, 1938)
- Schroeder, Henry A, M D Hypertension Division, Department of Internal Medicine, Washington University, 610 S Kingshighway, St Louis 10, Mo (1, 1917)
- Schubert, Maxwell, A M, Ph D Department of Therapeutics, N Y U College of Medicine, 177 First Avenue, New York 10, N Y Research Associate in Therapeutics (3, 1917)
- Schuck, Cecelia, Ph D Purdue University, Lafayette, Ind Professor of Nutrition, Department of Home Economics (3, 1911)
- Schultz, Edwin William, M D 713 Cooksey Lane, Stanford University, Calif Professor of Bacteriology and Experimental Pathology (4, 1927, 6, 1928)
- Schultz, W H, Ph D 3102 18th St, N W, Washington, D C Professor of Pharmacology, Emeritus, University of Maryland (1, 1907, 3, 1909)
- Schultze, Max O, Ph D Division of Agricultural Biochemistry, Univ of Minnesota, St Paul 5, Minn Professor (2, 1938)
- Schweizer, Malvina, Ph D Washington Square College of Arts and Sciences, New York University, New York, N Y Instructor in Biology (1, 1944)
- Schwimmer, Sigmund, M S, Ph D Luzerne Research Laboratory, 800 Buchanan Street, Albany 6, Calif Chemist, U S Department of Agriculture, U S Bureau of Agricultural and Industrial Chemistry (2, 1917)
- Scott, Charles Covert, Ph D, M D The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Ind Pharmacologist (3, 1945)
- Scott, David Alymer, M A, Ph D Connaught Laboratories, University of Toronto, Toronto 5, Ontario, Canada Research Member (2, 1935)
- Scott, Ernest L, Ph D 64 South St, Bogota, N J Associate Professor of Physiology, Emeritus, Columbia University (1, 1914, 2, 1915)
- Scott, Frederick Hughes, Ph D, Sc D, M B University of Minnesota, Minneapolis Professor of Physiology, Emeritus (1, 1908, 2, 1909)
- Scott, John C, Ph D Hahnemann Medical College, Philadelphia, Pa Professor of Physiology and Head of the Department (1, 1936)
- Scott, R W, A M, M D City Hospital, Cleveland, O Professor of Clinical Medicine, Western Reserve University, Physician-in-chief, Cleveland City Hospital (1, 1917, 3, 1917)
- Scott, V Brown, Ph D, M D Inlow Clinic, Shelbyville, Ind Internist, Division of Medicine (1, 1941)
- Scott, W J Merle, M D University of Rochester Medical School, Rochester, N Y Associate Professor of Surgery (4, 1925)
- Scott, W W, Ph D, M D Brady Urological Inst, The Johns Hopkins Hospital, Baltimore 5, Md (1, 1913)
- Studi, John Vincent, Ph D Pyridium Corporation, Nepera Park, Yonkers 2, N Y Director of Research (2, 1912, 5, 1945)
- Seager, Lloyd D, M S, M D Woman's Medical College of Pennsylvania, East Falls, Philadelphia Professor of Pharmacology and Toxicology (3, 1939)
- Sealock, Robert R, Ph D Iowa State College, Ames Associate Professor of Chemistry (2, 1910, 5, 1941)
- Seastone, C V, Jr, M D University of Wisconsin Medical School, Madison Professor of Medical Bacteriology (6, 1939)
- Sebrell, W H, Jr, M D National Institute of Health, Bethesda, Md Chief, Division of Physiology (2, 1938, 5, 1937)
- Seecof, David P, M D 1970 Daly Ave, Bronx, New York City (4, 1927)
- Seegal, David, M D Welfare Island, New York City Director, Research and Clinical Service, First Division, Goldwater Memorial Hospital, Associate Professor of Medicine, Columbia University (6, 1930)
- Seegers, Walter H, Ph D Wayne University College of Medicine, Detroit 26, Mich Professor of Physiology (1, 1917, 2, 1941)
- Seever, Maurice Harrison, Ph D, M D University of Michigan School of Medicine, Ann Arbor Professor of Pharmacology and Chairman of the Department (1, 1933, 3, 1930)
- Segaloff, Albert, M D Alton Ochsner Medical Foundation, 3503 Prytania St, New Orleans, La Director of Endocrine Research (4, 1946)
- Seibert, Florence B, Ph D, Sc D, LL D Henry Phipps Institute, University of Pennsylvania, 7th and Lombard Sts, Philadelphia Associate Professor of Biochemistry (2, 1925)
- Seidell, Atherton, M S, Ph D 2301 Connecticut Ave, Washington, D C Special Expert, National Institute of Health (2, 1924)
- Seifter, Joseph, M D Wyeth Institute of Applied Biochemistry, Philadelphia, Pa Chief Pharmacologist (3, 1940)
- Seifter, Sam, M S, Ph D 350 Henry St, Brooklyn 2, N Y Assistant Professor of Biochemistry, Long Island College of Medicine (2, 1946)
- Selkurt, Ewald E, Ph D School of Medicine Western Reserve University, Cleveland 6, O Senior Instructor in Physiology (1, 1945)
- Selle, Wilber Arthur, Ph D Medical School, University of Texas, Galveston Professor of Physiology (1, 1938)
- Sellers, E A, M D Department of Pharma

- cology, University of Toronto, Ontario, Canada *Assistant Professor* (1, 1947)
- Selye, Hans, M D , Ph D , D Sc , F R S (c )  
Inst of Experimental Medicine and Surgery,  
Univ of Montreal, Montreal, Canada *Professor  
and Director* (1, 1934)
- Sendroy, Julius, Jr , M A , Ph D Mercy Hospi-  
tal, 2537 Prairie Ave , Chicago, Ill *Professor of  
Chemistry and Chairman of the Department of  
Experimental Medicine, Loyola University School  
of Medicine* (2, 1928)
- Sevag, M G , Ph D Department of Bacteri-  
ology, University of Pennsylvania School of  
Medicine, Philadelphia *Assistant Professor of  
Biochemistry in Bacteriology* (6, 1941)
- Sevringhaus, Elmer L , M A , M D Hoffmann-  
LaRoche, Inc , Nutley 10, N J *Director of  
Clinical Research, Consultant in Endocrinology  
and Nutrition, Gouverneur Hospital, New York  
City* (2, 1923, 5, 1939)
- Shaffer, Morris F , D Phil Department of Pathol-  
ogy and Bacteriology, School of Medicine, Tulane  
University of Louisiana, New Orleans *Associate  
Professor* (4, 1939, 6, 1937)
- Shaffer, Philip A , Ph D Washington University  
Medical School, St Louis 40, Mo *Distinguished  
Service Professor of Biological Chemistry, Mem-  
ber National Academy of Sciences* (2, 1906, 5,  
1935)
- Shanes, Abraham M , M S , Ph D Dept of  
Physiology and Biophysics, Georgetown Univ  
School of Medicine, Washington 7, D C (1, 1946)
- Shank, Robert E , M D The Public Health  
Research Institute of The City of New York,  
Inc Foot of East 15th Street, New York 9,  
N Y *Associate, Division of Nutrition and  
Physiology* (2, 1947)
- Shannon, James A , Ph D , M D Squibb Insti-  
tute for Medical Research, New Brunswick, N J  
*Director, Squibb Institute for Medical Research*  
(1, 1933, 3, 1945)
- Shapiro, Herbert, Ph D National Institute of  
Health, Bethesda 14, Md (1, 1937)
- Sharpless, George R , M S , Sc D Lederle  
Laboratories, Pearl River, N Y *Research  
Biochemist* (5, 1942)
- Shaw, J C , M S , Ph D Department of Dairy  
Husbandry, University of Maryland, College  
Park, Md *Professor* (1, 1947)
- Shaw, Myrtle, M S , Ph D 11 S Lake Ave ,  
Albany, N Y *Senior Bacteriologist, Division  
of Laboratories and Research, New York State  
Department of Health* (6, 1937)
- Shay, Harry, M D Samuel S Fels Fund, Medical  
Tower, Philadelphia, Penna *Director, Medical  
Research Laboratory* (1, 1944)
- Shear, Murray, J , Ph D National Cancer In-  
stitute, Bethesda, Md *Chief Biochemist and  
Chairman, Chemotherapy Section* (2, 1930)
- Sheard, Charles, A M , Ph D Mayo Foundation,  
Rochester, Minn *Chief of the Division of  
Physics and Biophysical Research and Professor  
of Physiological Optics and Biophysics, Univer-  
sity of Minnesota* (1, 1925)
- Sheehan, Donal, M D , D Sc New York Uni-  
versity College of Medicine, First Ave , New  
York City *Professor of Anatomy and Director  
of Anatomical Laboratories* (1, 1938)
- Shelley, Walter Brown, Ph D 1214 Perkins St ,  
Chester, Pa University of Pennsylvania Medi-  
cal School *Instructor of Physiology* (1, 1946)
- Shemin, David, A M , Ph D Columbia University,  
College of Physicians and Surgeons, 630 W 168th  
St , New York City *Assistant Professor of Bio-  
chemistry* (2, 1944)
- Sheppard, Fay, M S University of Oklahoma  
Medical School, Oklahoma City *Instructor in  
Biochemistry* (2, 1936)
- Sherman, Henry C , A M , Ph D , Sc D Colum-  
bia University, New York City *Mitchell Pro-  
fessor Emeritus of Chemistry, Member, National  
Academy of Sciences* (1, 1923, 2, 1906, 5, 1933)
- Sherwin, Carl Paxson, Sc D , M D , Dr P H ,  
LL D 6 Cristensen Rd , Scarsdale, N Y  
*Director of Metabolic Service, St Vincent's  
Hospital, Associate Physician, French Hospital*  
(1, 1919, 2, 1917)
- Sherwood, Noble P , Ph D , M D 1801 Indiana  
St , Lawrence, Kan *Professor of Bacteriology,  
University of Kansas* (6, 1928)
- Sherwood, Thomas Cecil, M A , Ph D , M D  
1824 Robert St , New Orleans, La Southern  
Baptist Hospital *Staff Member, Internal Medi-  
cine* (1, 1935)
- Shettles, Landrum B , Ph D , M D College of  
Physicians and Surgeons, Columbia Presby-  
terian Medical Center, Box 330, 622 W 168th  
St , New York City (1, 1946)
- Shideman, Frederick E , B A , Ph D Dept of  
Pharmacology, University of Michigan, Ann  
Arbor *Instructor of Pharmacology* (3, 1944)
- Shimkin, Michael Boris, M D University of  
California Medical School, San Francisco  
*Director, Laboratory of Experimental Oncology*  
(1, 1910)
- Shupley, Reginald A , M D Western Reserve  
University School of Medicine, Cleveland 6, O  
*Assistant Professor of Medicine* (1, 1945)
- Shupley, Robert E , M D Lilly Laboratory for  
Clinical Research, Indianapolis City Hospital,  
Indianapolis, Ind (1, 1945)
- Shlaer, Simon, M A , Ph D Box 1663, Los  
Alamos, New Mexico (1, 1938)
- Shock, Nathan W , Ph D Section on Gerontol-  
ogy, U S Public Health Service, Baltimore  
City Hospitals, Baltimore 24, Md *Chief,  
Section on Gerontology, U S Public Health*

- Service, National Institute of Health, Bethesda, Md (1, 1912)
- Shoenaker, Harold A, M S, Ph D University of Oklahoma School of Medicine, 801 E 13th St, Oklahoma City Assistant Dean, Professor of Pharmacology (3, 1911)
- Shope, Richard E, M D Department of Animal and Plant Pathology, The Rockefeller Institute, Princeton, N J Member (1, 1931)
- Shorr, Ephraim, B A, M D The New York Hospital, 525 East 68th St, New York City Assistant Professor of Medicine Cornell University Medical College, Assistant Attending Physician, The New York Hospital (1, 1931, 3, 1912)
- Shwartzman, Gregory, M D 230 E 50th St, New York City Head of Department of Bacteriology, Mount Sinai Hospital, Clinical Professor of Bacteriology, Columbia University (4, 1929, 6, 1930)
- Sichel, F J M, Sc M, Ph D College of Medicine, University of Vermont, Burlington Associate Professor of Physiology (1, 1939)
- Sickles, Grace M, B A 2201 Twelfth St, Troy, N Y Associate Bacteriologist, Division of Laboratories and Research, New York State Department of Health (6, 1932)
- Sickles, Gretchen R, A B Division of Laboratories and Research, New York State Department of Health, Albany, N Y Assistant Bacteriologist (6, 1937)
- Siebenmann, Charles O, Ch L, D Eng Connaught Medical Research Laboratories, Univ of Toronto, Toronto 5, Ontario, Canada Research Associate (3, 1946)
- Siebert, Walter J, M D DePaul Hospital, St Louis 13, Mo Director of Laboratories and Pathologist of DePaul and Lutheran Hospitals, St Louis, and of St Joseph Hospital, Elton, Ill, St Elizabeth's Hospital, Belleville, Ill, St Francis Hospital, Washington, Mo (1, 1932)
- Silberberg Martin, M D Snodgrass Laboratory of Pathology, City Hospital, 1130 Carroll St, St Louis 4, Mo Instructor in Pathology, Washington University, School of Medicine (4, 1941)
- Silberberg, Ruth, M D Snodgrass Laboratory of Pathology, City Hospital, 1430 Carroll St, St Louis 4, Mo Instructor in Pathology, Washington University, School of Medicine (4, 1944)
- Silvette, Herbert, M S, Ph D University of Virginia Medical School, University Acting Head of Pharmacology (1, 1933, 3, 1940)
- Simon, Frank A, M D 332 West Broadway, Louisville, Ky (6 1934)
- Simonds, James P, Ph D, M D Northwestern University Medical School, 234 E Pearson St, Chicago 2, Ill Emeritus Professor of Pathology (4, prior to 1920)
- Simonson, Ernst, M D c/o Laboratory of Physiological Hygiene, Stadium South Tower, University of Minnesota, Minneapolis 11 Associate Professor of Physiology (1, 1911)
- Simpson, Miriam E, M A, Ph D, M D Div of Anatomy, Univ of Calif, Berkeley, Calif Professor of Anatomy (1, 1916)
- Sinclair, Robert Gordon, Ph D, F R S C Queen's University, Kingston, Ont, Canada Professor of Biochemistry (2, 1931)
- Sizer, Irwin W, Ph D Massachusetts Institute of Technology, Cambridge Associate Professor of Physiology (1, 1911)
- Skinner, John Taylor, M S, Ph D c/o The Grapette Co, Camden, Arkansas Chief Chemist (2, 1916)
- Slaughter, Donald, M D Univ of South Dakota, School of Medicine, Vermillion, S D Dean (3, 1938)
- Slonaker, James R, Ph D 334 Kingsley Ave, Palo Alto, Calif Professor of Physiology, Leland Stanford Junior University (1, 1917)
- Smadel, Joseph Edwin, M D Department of Virus and Rickettsial Diseases, Army Medical Department, Research and Graduate School, Washington 12, D C Scientific Director (4, 1910, 6, 1937)
- Small James C, M D 101 S 39th St, Philadelphia, Pa Associate in Medicine, Graduate School of Medicine, University of Pennsylvania (1, 1927)
- Smetana, Hans F, M D Army Institute of Pathology, 7th St, and Independence Ave, Washington 25, D C (4, 1931)
- Smith Arthur H, M S, Ph D Wayne University College of Medicine, Detroit 26, Mich Professor of Physiological Chemistry (1, 1923, 2, 1921, 5, 1933)
- Smith, Austin Edward, M D, C M, M Sc (Med) American Medical Association, 535 N Dearborn St, Chicago, Ill Secretary of the Council on Pharmacy and Chemistry, American Medical Association, Professorial Lecturer, Dept of Pharmacology, University of Chicago (3, 1942)
- Smith, Clarence A, M S, Ph D Standard Brands, Inc, 595 Madison Ave, New York City Technical Director, Agricultural Department (1, 1921)
- Smith, David T Duke Hospital, Durham, N C (5, 1943)
- Smith, Dietrich Conrad, A M, Ph D University of Maryland School of Medicine, Lombard and Greene Sts, Baltimore Associate Professor of Physiology (1, 1937)
- Smith, Douglas C, M S, Ph D Department of Physiology, St Louis University School of Medicine St Louis 4, Mo Senior Instructor (1, 1947)

- Smith, Elinor Van Dorn, Ph D 5 Middle St, Hadley, Mass *Associate Professor of Bacteriology, Smith College* (6, 1940)
- Smith, Elizabeth R B, Ph D c/o Dr Paul K Smith, 1335 H St, N W, Washington 5, D C (2, 1938)
- Smith, Emil L, Ph D School of Medicine, Univ of Utah, Salt Lake City 1, Utah *Associate Professor of Biochemistry* (2, 1946)
- Smith, Erma A, M A, Ph D, M D College Station, Durham, N C (1, 1928)
- Smith, George H, M A, Ph D, M A (hon), Sc D School of Medicine, Yale University, New Haven, Conn *Professor of Immunology and Assistant Dean, Chairman, Department of Bacteriology, Yale University* (6, 1918)
- Smith, H P, M S, M D Columbia Univ, Coll of Physicians and Surgeons, 630 West 168th St, New York 32, N Y *Delafield Professor of Pathology* (1, 1937, 4, 1925)
- Smith, Homer W, M S (hon), Sc D 477 First Ave, New York City *Professor of Physiology, New York University College of Medicine, Member, National Academy of Sciences* (1, 1923, 2, 1930)
- Smith, Janice M, M S, Ph D Department of Home Economics, University of Illinois, Urbana, Ill *Professor and Chief of Nutrition* (5, 1947)
- Smith, John R, A M, M D Washington University School of Medicine, St Louis 10, Mo *Assistant Professor of Medicine* (1, 1947)
- Smith, Lawrence Weld, M D 119 E 26th St, New York 10, N Y (4, 1927)
- Smith, Lee Irvin, A M, Ph D School of Chemistry, University of Minnesota, Minneapolis *Professor and Chief, Division of Organic Chemistry* (2, 1942)
- Smith, Margaret Cammack, A M, Ph D El Encanto Estates, Tucson, Arizona (2, 1935, 5, 1933)
- Smith, Maurice I, M D National Institute of Health, Bethesda 14, Md *Chief Pharmacologist, U S Public Health Service* (1, 1920, 3, 1916)
- Smith, Paul K, Ph D Department of Pharmacology and Therapeutics, George Washington Univ School of Medicine, 1335 H St, N W, Washington 5, D C *Professor of Pharmacology and Executive Officer of the Department* (2, 1937, 3, 1937)
- Smith, Paul W, M S, Ph D School of Medicine, University of Oklahoma, 801 E 13th St, Oklahoma City *Assistant Professor of Pharmacology* (1, 1933)
- Smith, Philip Edward, M S, Ph D 630 W 168th St, New York City *Professor of Anatomy, Columbia University, Member of the National Academy of Sciences* (1, 1923)
- Smith, Ralph G, M D, Ph D Tulane University, Station 20, New Orleans, La *Professor of Pharmacology* (3, 1929)
- Smith, R Blackwell, Jr, B S, M S, Ph D Medical College of Virginia, Richmond 19, Va *Lecturer in Pharmacology* (3, 1944)
- Smith, Sedgwick E, Ph D Dept Animal Husbandry, Cornell University, Ithaca, N Y *Animal Physiologist* (5, 1945)
- Smith, Susan Gower, M A Duke University, Durham, N C *Associate, Department of Medicine and Nutrition, School of Medicine* (5, 1939)
- Smith, Sybil L, A M Principal Experiment Station Administrator, Office of Experiment Stations, U S D A, Washington, D C (5, 1940)
- Smith, Wilbur Kenneth, M D University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd, Rochester, N Y *Associate Professor of Anatomy* (1, 1939)
- Smith, Willie W, M A, Ph D Bethesda, Md *Associate Physiologist, National Institute of Health* (1, 1941)
- Smithburn, Kenneth C, M D Yellow Fever Research Institute, P O Box 49, Entebbe, Uganda, British East Africa *Staff Member, International Health Division of The Rockefeller Foundation* (6, 1937)
- Smolens, Joseph, B S Wyeth Research Inst, 900 N Broad St, Philadelphia, Pa *Head, Dept of Immunology* (6, 1943)
- Smythe, C V, M S, Ph D 5000 Richmond St Philadelphia, Pa *Head of Biochemistry, Rohm & Haas Company* (2, 1934)
- Snell, Albert M, M D Mayo Clinic, Rochester, Minn *Head of Section on Medicine at Mayo Clinic, Professor in Medicine, Mayo Foundation Graduate School, University of Minnesota* (4, 1930)
- Snell, Esmond E, M A, Ph D University of Wisconsin, Madison 6 *Professor of Biochemistry* (2, 1942, 5, 1946)
- Snyder, Charles D, M S, Ph D 4709 Keswick Rd, Baltimore 10, Md *Professor Emeritus of Experimental Physiology, Johns Hopkins Univ* (1, 1907)
- Snyder, Franklin Faust, M D Boston Lying-In Hospital, Boston, Mass (1, 1936)
- Sobel, Albert E, Ch E, M A, Ph D Jewish Hospital of Brooklyn, Prospect Place and Classon Ave, Brooklyn, N Y *Director of Chemical Laboratories, Jewish Hospital of Brooklyn, Adjunct Professor of Chemistry, Polytechnic Institute of Brooklyn* (2, 1939)
- Sobotka, Harry H, Ph D Mount Sinai Hospital, Fifth Ave and 100th St, New York City *Head, Department of Chemistry* (2, 1932, 5, 1933)
- Solandt, Donald Young, M A, M D, Ph D University of Toronto, Toronto, Ont, Canada



- Professor of Physiology in charge of Biophysics, Faculty of Medicine, Professor of Physiological Hygiene and Head of Department, School of Hygiene* (1, 1937)
- Soler, Mayo H., M D University of California Medical School, The Medical Center, San Francisco Associate Professor of Medicine and Assistant Dean (1, 1913)
- Sollmann, Torald, M D Sc D, LL D School of Medicine, Western Reserve University, 2109 Adelbert Rd., Cleveland, O Dean and Professor of Pharmacology and Materia Medica, Emeritus (1, 1902, 2, 1906, 3, 1908)
- Solotorovsky, Morris, M S 203 W 5th St., Plainfield, N J *Merck Institute for Therapeutic Research, Rahway, N J* (6, 1916)
- Somogyi, Michael, Ph D 216 S Kingshighway, St Louis, Mo Biochemist, Jewish Hospital of St Louis (2, 1927)
- Soskin, Samuel, M D, M A, Ph D Michael Reese Hospital, 29th St and Ellis Ave., Chicago 10, Ill Medical Director and Director of Research Institute, Michael Reese Hospital, Dean, Michael Reese Hospital Postgraduate School, Professorial Lecturer in Physiology, University of Chicago (1, 1930, 5, 1933)
- Soule, Malcolm H., Sc D, LL D University of Michigan, Ann Arbor Professor of Bacteriology and Chairman of the Department of Bacteriology (4, 1927, 6, 1925)
- Spain, Will C., M D, F A C P 116 E 53rd St., New York City Clinical Professor of Medicine, Post Graduate Medical School, Columbia University (6, 1923)
- Speelman, C R, M A, Ph D Dept of Physiology Univ of Pennsylvania School of Medicine, Philadelphia, Pa (1, 1940)
- Specht, Heinz, Ph D National Institute of Health, Rockville Pike, Bethesda, Md Associate Research Physiologist (1, 1941)
- Sperry, Roger W., Ph D Dept of Anatomy, University of Chicago, Chicago 37, Ill (1, 1945)
- Sperry, Warren M., M S, Ph D 722 W 168th St., New York City Principal Research Biochemist, New York State Psychiatric Institute (2, 1929, 5, 1933)
- Spiegel, Ernest A., M D Temple University School of Medicine, Broad and Ontario Sts., Philadelphia, Pa Professor of Experimental Neurology (1, 1936)
- Spiegel-Adolf, Mona, M D Temple University School of Medicine, Broad and Ontario Sts., Philadelphia, Pa Professor and Head of Department of Colloid Chemistry (2, 1933)
- Spiegelman, Sol, Ph D Washington Univ School of Medicine, St Louis, Mo Instructor in Bacteriology (1, 1946)
- Spies, Tom D., M D Hillman Hospital, Birmingham, Ala Director, Nutrition Clinic (3, 1911, 1, 1910, 5, 1938)
- Spink, Wesley W., M D University of Minnesota Hospital, Minneapolis Associate Professor of Medicine, University of Minnesota Medical School (3, 1910, 4, 1910, 6, 1910)
- Spohn, Adelaide, M S, Ph D Elizabeth McCormick Memorial Fund, 318 N Dearborn St., Chicago, Ill (5, 1933)
- Spoor, Herbert J., Ph D Captain, MC, AUS Medical Department Field Research Laboratory, Fort Knox, Ky Research physician (1, 1915)
- Sproul, Edith E., M D Dept of Pathology, American Univ of Beirut, Beirut, Lebanon Professor of Pathology (1, 1911)
- Sprunt, Douglas H., M D, M S Univ of Tennessee, Memphis Professor of Pathology (4, 1934, 6, 1936)
- Stadie, William C., M D 821 Maloney Clinic, 36th and Spruce Sts Philadelphia, Pa Professor of Research Medicine, University of Pennsylvania (2, 1922)
- Stanley, Wendell M., M S, Ph D, Sc D, LL D Rockefeller Institute for Medical Research, Princeton, N J Member, Member, National Academy of Sciences (2, 1936)
- Stannard, James Newell, Ph D National Institute of Health, U S Public Health Service, Bethesda 11 Md Senior Pharmacologist (1, 1938)
- Stare, Fredrick J., Ph D, M D 695 Huntington Ave., Boston 15, Mass Professor of Nutrition, Harvard University (2, 1937, 5, 1912)
- Starr, Isaac, B S, M D 817 Maloney Clinic, Hospital of the University of Pennsylvania, Philadelphia Dean of the School of Medicine, Professor of Therapeutic Research (1, 1929, 3, 1942)
- Stavraky, George W., M D, C M, M Sc Medical School, University of Western Ontario, London, Ont, Canada Associate Professor of Physiology (1, 1937, 3, 1944)
- Stead, Eugene A., Jr M D Department of Medicine, Duke University, Durham, N C (1, 1945)
- Stearns, Genevieve, Ph D College of Medicine, State University of Iowa, Iowa City Research Professor of Pediatrics (2, 1932, 5, 1937)
- Steel, Matthew, Ph D Long Island College of Medicine, 350 Henry St., Brooklyn, N Y Professor of Biological Chemistry (2, 1909)
- Steele, J Murray, M D Thrd (N Y U) Research Division Goldwater Memorial Hosp., Welfare Island, New York City Associate Professor of Medicine, New York University, Director 3rd (New York University) Medical Division of Welfare Hospital (1, 1936)
- Steenbock, Harry, M S, Ph D, Sc D Univer-

- sity of Wisconsin, Madison *Professor of Biochemistry* (2, 1912, 5, 1933)
- Steggerda, F R**, M A, Ph D 416 Natural History Building, University of Illinois, Urbana *Associate Professor of Physiology* (1, 1934)
- Stehle, Raymond Louis**, A M, Ph D Faculty of Medicine, McGill University, Montreal, Canada *Professor of Pharmacology* (2, 1920, 3, 1922)
- Steigmann, Frederick**, M S, M D 348 S Hamlin Ave, Chicago, Ill *Associate in Medicine, College of Medicine, University of Illinois, Associate Attending Physician, Cook County Hospital* (3, 1942)
- Steiman, S E**, M A, Ph D, M D 3 Chestnut St, Lynn, Mass *Assistant Physician, Metropolitan State Hospital, Waltham, Mass* (1, 1939)
- Stein, George J**, M S, Ph D Army Medical Center, Washington, D C *Chief, Research Section, Veterans Division, Army Medical Department of Research and Graduate School* (6, 1947)
- Stein, William Howard**, Ph D The Rockefeller Institute for Medical Research, 66th and York Ave, New York 21, N Y *Associate in Chemistry* (2, 1946)
- Steinbach, H Burr**, M A, Ph D Dept of Zoology, University of Minnesota, Minneapolis (1, 1934)
- Steinberg, Bernhard**, M D Toledo Hospital Institute of Medical Research, Toledo, O *Director of the Toledo Hospital Institute of Medical Research, Director of Clinical and Morbid Pathological Laboratories, The Toledo Hospital, Surgeon, U S P H (inactive)* (4, 1928, 6, 1946)
- Steiner, Paul E**, M D The University of Chicago, Chicago, Ill *Associate Professor of Pathology* (4, 1939)
- Steinhardt, Jacinto**, A M, Ph D 1548 East-West Highway, Silver Spring, Md *Director of Research, Project 6397, Mass Institute of Technology* (2, 1939)
- Steinhaus, Arthur H**, M S, Ph D, M P E 5315 Drexel Ave, Chicago, Ill *Professor of Physiology, George Williams College, Hyde Park* (1, 1928)
- Stetten, Marjorie R**, Ph D Harvard Medical School, 25 Shattuck Street, Boston 15, Mass *Research Fellow in Biological Chemistry* (2, 1947)
- Stekol, Jakob A**, M A, D Sc The Lankenau Hospital Research Institute, Philadelphia 30, Pa *Associate Member* (2, 1936)
- Stern, Kurt G**, Ph D 85 Livingston St, Brooklyn, N Y *Lecturer in Chemistry, Polytechnic Institute* (2, 1938)
- Stetten, DeWitt, Jr**, M D, Ph D Harvard Medical School, 25 Shattuck St, Boston 15, Mass *Assistant Professor* (2, 1944)
- Stetten, Marjorie Roloff**, Ph D Harvard Medical School, 25 Shattuck St, Boston 15, Mass *Research Fellow in Biological Chemistry* (2, 1947)
- Stevens, S Smith**, Ph D Emerson Hall, Harvard University, Cambridge, Mass *Assistant Professor of Psychology* (1, 1937)
- Stewart, Dorothy R**, M S, Ph D Rockford College, Rockford, Ill (1, 1947)
- Stewart, Fred W**, M D Memorial Hospital, 444 E 68th St, New York City *Pathologist, Associate Professor of Surgical Pathology, Cornell Medical School, Pathologist, New York State Department of Public Health, Division of Laboratories and Research* (4, 1928)
- Stewart, Harold L**, M D The National Cancer Institute, Bethesda, Md *Chief, Pathology Section* (4, 1936)
- Stewart, Winifred Bayard**, M D, M A 1930 Spruce St, Philadelphia, Pa *Professor of Neurology, Woman's Medical College of Pennsylvania* (1, 1941)
- Stiekney, J Clifford**, M S, Ph D West Virginia University School of Medicine, Morgantown *Assistant Professor of Physiology* (1, 1944)
- Stiebeling, Hazel K**, M A, Ph D United States Department of Agriculture, Washington, D C *Chief, Bureau of Human Nutrition and Home Economics* (5, 1933)
- Stier, Theodore J B**, Ph D Indiana University Medical School, Bloomington *Associate Professor of Physiology* (1, 1938)
- Still, Eugene U**, Ph D % Strong Cobb & Co, 2654 Lisbon Rd, Cleveland, O (1, 1929)
- Stillman, Ernest G**, M D 45 E 75th St, New York City (6, 1930)
- Stummel, Benjamin F**, Ph D Rees Stealy Medical Research Fund, Ltd, 2001 Fourth Avenue, San Diego, Calif *Research Biochemist* (2, 1947)
- Stock, Aaron H**, M D School of Medicine, University of Pittsburgh, Pittsburgh, Penn *Assistant Professor of Bacteriology and Immunology* (6, 1947)
- Stockton, Andrew Benton**, M D Barracks Dispensary, U S Naval Supply Depot, Oakland, Calif *Assistant Clinical Professor of Medicine, Stanford Medical School, Commander, (M C) U S N R* (3, 1931)
- Stokinger, Herbert B**, Ph D 250 Meigs Street, Rochester, N Y *Chief, Industrial Hygiene Section, Atomic Energy Commission, Rochester, N Y* (6, 1947)
- Stokstad, E L Robert**, Ph D Lederle Laboratories, Pearl River, N Y *Chemist* (2, 1947, 5, 1942)
- Stoland, O O**, M S, Ph D 1845 Learned Ave, Lawrence, Kan *Professor of Physiology and Pharmacology, University of Kansas* (1, 1913)

- Stone, William E, Ph D Department of Physiology, University of Wisconsin, Madison Assistant Professor of Physiology (1, 1915)
- Stormont, Robert T, Ph D, M D Medical Division, Food and Drug Administration, Washington, D C (3, 1941)
- Storvick, Clara A, M S, Ph D School of Home Economics, Oregon State College, Corvallis, Ore Associate Professor of Foods and Nutrition (5, 1947)
- Stotz, Elmer H, Ph D University of Rochester School of Medicine and Dentistry, Rochester 7, N Y Professor of Chemistry (2, 1939)
- Stoughton, Roger W, M S, Ph D Mallinckrodt Chemical Works, 3600 N Second St, St Louis, Mo Research Chemist (3, 1939)
- Strong, Frank M, M A, Ph D Department of Biochemistry, University of Wisconsin, Madison Associate Professor of Biochemistry (2, 1941)
- Struch, Harold Carl, Ph D School of Medicine, The Creighton University, 302 N 11th St, Omaha 2, Nebr (1, 1940)
- Stuart, Charles A, M Sc, Ph D 372 Lloyd Ave, Providence, R I Associate Professor of Biology, Brown University (6, 1935)
- Sturgis, Cyrus Cressey, M D Simpson Memorial Institute, Ann Arbor, Mich Director, Thomas Henry Simpson Memorial Institute for Medical Research, Chairman, Department of Medicine, University Hospital, and Professor of Medicine, University of Michigan (4, 1927)
- Stutzman, Jacob W, Ph D M D Department of Pharmacology, Boston University School of Medicine, 50 E Concord St, Boston, Mass Associate Professor of Pharmacology, (1, 1916)
- Subbarow, Y, Ph D Lederle Laboratories, Pearl River, N Y (2, 1939)
- Sugg, John Y, Ph D Cornell University Medical College, 1300 York Ave, New York City Associate Professor of Bacteriology and Immunology (6, 1938)
- Sulkin, S Edward, Ph D Southwestern Medical Foundation, Dallas, Texas Professor of Bacteriology and Immunology (6, 1944)
- Sullivan, Michael Xavier, Ph D Chemo Medical Research Institute, Georgetown University, 37th & O Sts, N W, Washington, D C Director and Research Professor of Chemistry (2, 1909)
- Sulzberger, Marion B, M D 962 Park Ave, New York 28, N Y Associate Clinical Professor of Dermatology and Syphilology, N Y Post Graduate Medical School of Columbia Univ, Assoc Director, Skin and Cancer Unit of N Y Post-Graduate Hospital (6, 1936)
- Summerson, William H, M A, Ph D Medical Division, Army Chemical Center, Md Chief, Biochemistry Section (2, 1942)
- Sumner, J B, A M, Ph D Savage Hall, Ithaca, N Y Professor of Biochemistry, Cornell University (2, 1919)
- Sunderman, F William, M D, Ph D 2210 Delancey St, Philadelphia 3, Pa Director of Laboratory of Clinical Medicine and Professor of Clinical Pathology, Temple University School of Medicine (2, 1931)
- Sundstroem, Edward S, M D University of California, Berkeley Professor of Biochemistry (2, 1919)
- Sure, Barnett, M S, Ph D University of Arkansas, Fayetteville Head of Department and Professor of Agricultural Chemistry (2, 1923, 5, 1933)
- Sutherland, George F, CM, M D, M Sc Duke University School of Medicine, Durham, N C (1, 1939)
- Sutton, T Scott, M Sc, Ph D Ohio State University, Columbus Professor, Ohio State University, Associate, Ohio Agricultural Experiment Station, Director, Institute of Nutrition and Food Technology (5, 1936)
- Svirbely, Joseph L, Ph D Monsanto Chemical Co, Central Research Department, 1601 W First St, Dayton 7, Ohio Pharmacologist (3, 1915)
- Swain, Robert E, M S, Ph D, LL D 634 Mirada Ave, Stanford University, Calif Professor Emeritus of Chemistry (2, 1909)
- Swann, Howard G, M S, Ph D Dept of Physiology, University of Texas Medical School, Galveston Assistant Professor of Physiology, Captain, Aero Medical Laboratory, Wright Field, Dayton, O (1, 1940)
- Swanson, Pearl P, M S, Ph D Iowa State College, Ames Professor of Foods and Nutrition, Dept of Foods and Nutrition (5, 1933)
- Swanson, William W, M S, M D 2376 E 71st St, Chicago, Ill Assistant Professor of Pediatrics, Northwestern University (2, 1938)
- Sweeney, H Morrow, M S, Ph D School of Medical Sciences, University of South Dakota, Vermillion Professor of Physiology and Pharmacology and Head of the Department (1, 1939)
- Sweet, J E, A M, M D, Sc D Unadilla, N Y Emeritus Professor of Surgical Research, Cornell Medical College (1, 1913)
- Swift, Homer, M D, D Sc 888 Park Ave, New York City Member, Rockefeller Institute for Medical Research, Physician to The Hospital of The Rockefeller Institute for Medical Research (6, 1920)
- Swift, Raymond W, M S, Ph D Pennsylvania State College, State College Professor, Department of Animal Nutrition (5, 1934)
- Swingle, Wilbur Willis, Ph D Princeton University, Princeton, N J Professor of Biology (1, 1924)
- Sydenstricker, V P University of Georgia School

- of Medicine, Augusta *Professor of Medicine* (5, 1944)
- Sykes, Joseph F, M S A, Ph D U S Dept of Agriculture, Bureau of Dairy Industry, Beltsville, Md *Physiologist* (1, 1942)
- Syvertson, Jerome T, M D Louisiana State University School of Medicine, New Orleans *Head, Department of Microbiology* (4, 1940, 6, 1947)
- Szego, Clara M, M S, Ph D Department of Physiological Chemistry, Yale University School of Medicine, New Haven, Conn *Research Instructor* (1, 1946)
- Tabor, Herbert, M D Division of Physiology, National Institute of Health, U S Public Health Service, Bethesda 14, Md *Senior Assistant Surgeon* (3, 1947)
- Tainter, M L, M A, M D Sterling-Winthrop Research Institute, 33 Riverside Ave, Reins-selaer, N Y *Director of Research* (1, 1929, 3, 1927)
- Talbot, Samuel Armstrong, A M, M S, Ph D Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md *Instructor in Physiological Optics, Johns Hopkins University* (1, 1940)
- Taliaferro, William H, Ph D Department of Bacteriology, University of Chicago, Chicago, Ill *Eliakim H Moore Distinguished Service Professor of Parasitology and Dean of the Division of Biological Sciences* (6, 1930)
- Tannenbaum, Albert, M D Michael Reese Hospital, 29th St & Ellis Ave, Chicago, Ill *Director, Department of Cancer Research* (4, 1942)
- Tarver, Harold, M S, Ph D Division of Biochemistry, University of California, Berkeley, Calif *Assistant Professor of Biochemistry* (2, 1947)
- Tashiro, Shiro, Ph D, M D College of Medicine, University of Cincinnati, Cincinnati, O *Professor of Biochemistry* (1, 1913, 2, 1913)
- Tatum, Arthur L, M S, Ph D, M D University of Wisconsin, Madison *Professor of Pharmacology* (1, 1913, 3, 1919)
- Tatum, Edward L, M S, Ph D Yale University, New Haven, Conn *Professor of Microbiology* (2, 1947)
- Tauber, Henry, Ph D V D Research Laboratory, U S Marine Hospital, Staten Island, N Y *Biochemist, U S Public Health Service* (2, 1933)
- Taylor, Alonzo E, M D General Mills, Inc 400 2nd Ave S, Minneapolis, Minn *Director of Research Director Emeritus, Food Research Institute, Stanford University* (5, 1933)
- Taylor, Alton R, Ph D Parke, Davis Co, Detroit 32, Mich *Senior Research, Research Division* (2, 1947, 6, 1943)
- Taylor, Craig L, M A, Ph D Dept of Engineer-ing, Univ of Calif, Los Angeles, Calif *Associate Professor of Engineering* (1, 1945)
- Taylor, Fred A, Ph D 320 E North Ave, N S, Pittsburgh, Pa *Biochemist, Singer Memorial Laboratory* (2, 1933)
- Taylor, Haywood M, M S, Ph D Duke University School of Medicine, Durham, N C *Associate Professor of Biochemistry and Toxicology, Biochemist and Toxicologist to Duke Hospital* (4, 1942)
- Taylor, Henry Longstreet, Ph D University of Minnesota, Minneapolis *Assistant Professor of Physiology* (1, 1944)
- Taylor, John Fuller, Ph D Washington University School of Medicine, Euclid and Kingshighway, St Louis, Mo *Assistant Professor of Biological Chemistry* (2, 1944)
- Taylor, M Wight New Jersey Agricultural Experiment Station, New Brunswick *Assoc Biochem in Nutr, and Assoc Prof of Agr Biochem, Rutgers Univ* (5, 1944)
- Taylor, Norman Burke, M D, F R S (Can), M R C S (Eng), L R C P (Lon), F R C S (Edin), F R C P (Can) University of Toronto, 5, Ontario, Ont, Canada *Professor of Physiology* (1, 1922)
- Taylor, Robert D, M D Clinical Research Division, Cleveland Foundation, Cleveland 6, O *Member* (1, 1945)
- Teague, Robert S, Ph D, M D Dept of Pharmacology and Physiology, Medical College of Alabama, Birmingham 5, Ala *Associate Professor of Physiology and Pharmacology* (3, 1942)
- Templeton, Roy D, B S 5630 South Flores, San Antonio, Texas (1, 1935)
- Ten Broeck, Carl, M D The Rockefeller Institute for Medical Research, Department of Animal and Plant Pathology, Princeton, N J *Member* (4, 1932, 6, 1924)
- Tepperman, Jay, M D Dept of Pharmacology, Syracuse University School of Medicine, Syracuse, N Y *Associate Professor of Pharmacology* (1, 1944)
- Terplan, Kornel L, M D University of Buffalo, School of Medicine, Buffalo, N Y *Professor of Pathology* (4, 1935)
- Thannhauser, S J, M D, Ph D Pratt Diagnostic Hospital, 30 Bennet St, Boston, Mass *Professor of Clinical Medicine, Tufts Medical School, Associate Chief, Pratt Diagnostic Hospital* (2, 1937)
- Thayer, Sidney Allen, Ph D 1402 S Grand Blvd, St Louis 4, Mo *Associate Professor of Biochemistry, St Louis University School of Medicine* (2, 1933)
- Theiler, Max, M D Rockefeller Foundation, New York City *Member of Field Staff* (4, 1938)

- Thuenes, Clinton H., A M., M D., Ph D University of Southern California School of Medicine, Los Angeles *Professor of Pharmacology* (3, 1928)
- Thomas, Arthur W., Ph D Columbia University, New York City *Professor of Chemistry* (2, 1924)
- Thomas, Byron H., M S., Ph D Iowa State College, Ames *Professor and Head, Animal Chemistry and Nutrition, Iowa Agricultural Experiment Station* (5, 1933)
- Thomas, Caroline Bedell, M D The Johns Hopkins Hospital, Baltimore, Md *Associate Professor of Medicine, Johns Hopkins University School of Medicine* (1, 1939)
- Thomas, J Earl, M S., M D Jefferson Medical College, Philadelphia, Pa *Professor of Physiology* (1, 1922, 3, 1924)
- Thompson, Marvin R., Ph C., B Sc., M Ph., (Hon) Ph D 67 Greenwich Ave., Stamford, Conn (3, 1941)
- Thompson, Randall L., Sc D., M D Medical College of Virginia, Richmond, Va *Associate Professor of Bacteriology* (6, 1937)
- Thompson, William R., Ph D 1 Darrock Rd., Delmar, N Y *Senior Biochemist, Division of Laboratories and Research, New York State Department of Health* (2 1934)
- Thomson, David Landsborough, M A., Ph D., F R S C McGill University, Montreal, Canada *Professor of Biochemistry and Dean of the Faculty of Graduate Studies and Research* (2, 1929)
- Thorn, George Widmer, M D Peter Bent Brigham Hospital, Boston, Mass *Professor of Medicine of Harvard University* (1, 1939)
- Tillett, William S., M D., Sc D (hon) Department of Bacteriology, New York University College of Medicine, 477 First Ave., New York City *Professor of Medicine* (6, 1927)
- Tilt, Jennie, M S., Ph D Florida State College for Women, Tallahassee *Professor of Physiological Chemistry and Nutrition* (5, 1937)
- Tipson, R Stuart, Ph D., D Sc Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa *Senior Fellow, Department of Research in Pure Chemistry* (2, 1937)
- Tipton, Samuel R., Ph D Department of Zoology, University of Tennessee, Knoxville *Professor of Zoology* (1, 1940)
- Tisdall, Frederick F., M S., M D., M R C S., L R C P (London), F R C P (C) University of Toronto, Toronto, Canada *Associate Professor of Pediatrics, Department of Medicine, University of Toronto, Associate Physician, Hospital for Sick Children* (2, 1922, 5, 1933)
- Tislow, Richard, M D Schering Corporation, Bloomfield, N J *Director of Biological Laboratories* (1 1944)
- Titus, Harry W., A M., Ph D Lime Crest Research Lab, RFD #1, Newton, N J *Technical Counsellor and Director of Nutritional Research* (2, 1929, 5, 1933)
- Tobias, Julian M., M D University of Chicago, Chicago, Ill *Instructor in Physiology On leave to Medical Research Laboratory, Edgewood Arsenal, Md* (1, 1944)
- Tocantins, Leandro Maués, M D Jefferson Medical College, Philadelphia, Pa *Associate Professor of Medicine* (1, 1939)
- Todhunter, Elizabeth Neige, M Sc., Ph D., University of Alabama, University *Professor of Nutrition* (5, 1939)
- Tocannes, Gerrit, Ph D Lankenau Hospital, Philadelphia 30, Pa *Senior Member, Institute for Cancer Research* (2, 1931)
- Tolle, Chester D., Ph D Food and Drug Administration, Federal Security Agency, Washington, D C *Senior Biochemist* (5, 1942)
- Tonian, James E P., Ph D Dept of Pharmacology and Physiology, Univ of Utah School of Medicine, Salt Lake City (1, 1945)
- Tonkinson, Wray Joseph, M D Fort Logan Veteran's Hospital, Denver, Colorado *Chief of Labs, Assist Prof of Pathology, Univ of Colorado School of Medicine* (4, 1945)
- Tompkins, Edna H., M D Laboratory of Applied Physiology, Yale University, 52 Hillhouse Ave., New Haven, Conn *Research Associate, Associate Professor* (1, 1941)
- Toomey, John A., M D., LL B Division of Contagious Diseases, City Hospital, 3395 Scranton Rd., Cleveland, O *Professor of Pediatrics (Contagious Diseases), Western Reserve University School of Medicine* (6, 1943)
- Torda, Clara, Ph D., M D Cornell Medical College, New York City *Research Fellow in Department of Pharmacology* (1, 1943, 3, 1944)
- Toth, Louis A., M S., Ph D Dept of Physiology, Louisiana State University School of Medicine, New Orleans 13, La *Associate Professor of Physiology* (1, 1940)
- Totter, John R., M A., Ph D Univ of Arkansas School of Medicine, Little Rock, Ark *Associate Professor, Dept of Physiological Chemistry* (2, 1946)
- Tourtellotte, Dee, M S., D Sc Charles B Knox Gelatin Co, 4th and Erie Sts., Camden, N J (5, 1935)
- Tower, Sarah Sheldon, M D., Ph D Johns Hopkins University, Baltimore, Md *Instructor in Psychiatry* (1, 1932)
- Trager, Wilham, M D The Rockefeller Institute for Medical Research Department of Animal and Plant Pathology, Princeton, N J *Associate* (4, 1947)

- Traub, Frederick B**, M D 205 East 82nd St New York 28, N Y *Associate Bacteriologist, Jewish Hospital of Brooklyn* (6, 1946)
- Travell, Janet**, M D Cornell University Medical College, 1300 York Ave, New York City *Instructor in Pharmacology* (3, 1933)
- Travis, Lee Edward**, A M, Ph D University of Southern California, Los Angeles *Professor of Psychology and Director of the Psychological Center, Major, YAAF (Yuma, Ariz)* (1, 1929)
- Treadwell, Carleton R**, M S, Ph D Dept of Biochemistry, George Washington University School of Medicine, 1335 H St, Washington, D C *Associate Professor of Biochemistry* (2, 1944)
- Treffers, Henry P**, Ph D Yale Medical School, Department of Immunology, New Haven, Conn *Associate Professor of Immunology* (6, 1942)
- Trimble, Harry C**, M S, Ph D 25 Shattuck St, Boston, Mass *Assistant Professor of Biological Chemistry, Harvard Medical School* (2, 1929, 5, 1936)
- Tuft, Louis H**, M D 1530 Locust St, Philadelphia, Pa *Assistant Professor of Medicine, Temple University Medical School, Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital* (6, 1928)
- Tum Suden, Caroline**, M A, Ph D Department of Physiology, Mount Holyoke College, South Hadley, Mass (1, 1936)
- Tunturi, Archie Robert**, M S, Ph D Univ of Oregon Medical School, Portland, Ore *Assistant Professor of Anatomy* (1, 1946)
- Tuohy, Edward B**, M S, M D Mayo Clinic, Rochester, Minn *Assistant Professor of Anesthesiology, Mayo Foundation* (3, 1941)
- Turner, Abby H**, Ph D Mount Holyoke College, South Hadley, Mass *Professor of Physiology* (1, 1928)
- Tuttle, Waid Wright**, M A, Ph D State University of Iowa, Iowa City *Professor of Physiology* (1, 1925)
- Tweedy, Wilbur R**, Ph D Loyola University School of Medicine, 706 S Wolcott St, Chicago, Ill *Professor and Chairman, Department of Biological Chemistry* (2, 1931)
- Tyler, David B**, Ph D Department of Embryology, Carnegie Institution of Washington, Wolfe and Madison Sts, Baltimore 5, Md *Member of Staff* (1, 1943)
- Umbreit, Wayne W**, M Sc, Ph D Merck Institute for Therapeutic Research, Rahway, N J *Head, Enzyme Laboratory* (2, 1947)
- Unna, Klaus R W**, M D 1853 W Polk St, Chicago 12, Ill *Associate Professor, Dept of Pharmacology, Univ of Illinois Coll of Medicine* (1, 1941, 3, 1944, 5, 1942)
- Upton, Morgan**, M A, Ph D Dept of Psychology, Rutgers University, New Brunswick, N J (1, 1934)
- Urban, Frank**, Ph D, M D 302 Northern Building, Green Bay, Wis (2, 1932)
- Utter, Merton F**, Ph D Dept of Biochemistry, Western Reserve Univ, Cleveland, Ohio, *Associate Professor of Physiological Chemistry* (2, 1946)
- Vahlteich, Ella McCollum**, M A, Ph D 46 Hudson Ave, Edgewater, N J (5, 1933)
- Valle, J R**, M D Instituto Butantan, Caixa Postal 65, San Paulo, Brazil *Professor of Pharmacology, Escola Paulista de Medicina, Sio Paulo, Brazil* (3, 1947)
- Van Dyke, H B**, Ph D, M D 630 W 168th St, New York, N Y *Hosack Professor of Pharmacology, Columbia University, College of Physicians and Surgeons* (1, 1925, 3, 1927)
- van Harreveld, Anthonie**, M A, M D California Institute of Technology, Pasadena *Associate Professor of Physiology* (1, 1941)
- Van Liere, Edward J**, M S, M D, Ph D The School of Medicine, West Virginia University, Morgantown *Professor of Physiology and Dean* (1, 1927)
- Van Slyke, Donald D**, Ph D, Sc D, M D Rockefeller Institute for Medical Research, 66th St and York Ave, New York City *Member, Member, National Academy of Sciences* (2, 1908)
- van Wagenen, Gertrude**, Ph D Yale University School of Medicine, New Haven, Conn *Associate Professor* (1, 1932)
- van Wagtenonk, Willem J**, Ph D Dept of Zoology, Indiana University, Bloomington, Ind *Associate Professor of Zoology* (2, 1946)
- Van Winkle, Walton, Jr**, M D American Medical Assn, 535 N Dearborn St, Chicago 10, Ill (3, 1939)
- Vars, Harry M**, Ph D Harrison Department of Surgical Research, University of Pennsylvania Medical School, Philadelphia *Assistant Professor of Physiological Chemistry* (2, 1935, 5, 1935)
- Velick, Sidney Frederick** Dept of Biochemistry, Washington Univ School of Medicine, Euclid Ave and Kingshighway, St Louis 10, Mo *Assistant Professor of Biochemistry* (2, 1946)
- Vennesland, Birgit**, Ph D Dept of Biochemistry, University of Chicago, Chicago, Ill *Assistant Professor* (2, 1944)
- Venning, Eleanor H**, M S, Ph D University Clinic, Royal Victoria Hospital, Pine Ave, Montreal, Quebec, Canada *Assistant Professor of Medicine, McGill Univ* (2, 1938)
- Vestling, Carl Swensson**, Ph D Noyes Lab, Univ of Illinois, Urbana, Ill *Assistant Professor of Biochemistry* (2, 1946)
- Vickery, Hubert B**, M S, Ph D Connecticut

- Agricultural Experiment Station, New Haven  
*Lecturer in Physiological Chemistry, Yale University, Biochemist in Charge, Department of Biochemistry, Connecticut Agricultural Experiment Station, Member, National Academy of Sciences* (2, 1923)
- Victor, Joseph, M D Camp Detrick, Frederick, Md *Chief, Pathology Branch* (1, 1935)
- Virtue, Robert W, Ph D, M D 2131 E 11th Ave, Denver 10, Colo *Resident in Anesthesia, University of Iowa* (2, 1939)
- Visscher, Frank E, M S, Ph D Upjohn Co, Kalamazoo 99, Mich *Research Scientist, Department of Pharmacology and Endocrinology* (1, 1917)
- Visscher, Maurice B, Ph D, M D University of Minnesota, Minneapolis *Professor and Head of Dept of Physiology* (1, 1927)
- Voeightlin, Carl, Ph D Dept of Biochemistry and Pharmacology, University of Rochester School of Medicine and Dentistry, Rochester, N Y *Lecturer in Pharmacology* (1, 1908, 2, 1908, 3, 1908)
- von Haam, Emmerich, M D Ohio State University, Columbus *Professor of Pathology* (4, 1938)
- Von Oettingen, W F, M D, Ph D National Institute of Health, Division of Industrial Hygiene, Bethesda, Md *Principal Industrial Toxicologist* (3, 1925)
- Vorwald, Arthur J, Ph D, M D Sirrine Lake, N Y *Director of Research The Eduard L Traubau Foundation and Director of the Saranac Laboratory* (1, 1937)
- Vos, Bert J, Ph D, M D Division of Pharmacology, Food and Drug Administration, Washington, D C *Associate Pharmacologist* (3, 1941)
- Wachstein, Max, M D E A Horton Memorial Hospital, Middleton, N Y, *Director of the Laboratory Research Assistant, Division of Pathology, Mt Sinai Hospital New York, N Y* (4, 1947)
- Waddell, James, Ph D E I duPont de Nemours & Co, New Brunswick, N J *Director of the Biological Laboratory* (2, 1930, 5, 1935)
- Wadsworth, Augustus B, M D Manchester, Vermont (4, 1935, 6, 1920)
- Waelisch, Heinrich, M D, Ph D 722 West 168th St, New York 32, N Y *Associate Research Biochemist, N Y State Psychiatric Institute and Hospital, Assistant Professor of Biological Chemistry, Columbia University* (2, 1941)
- Wagman, Irving H, M A, Ph D Dept of Physiology, Jefferson Medical College Philadelphia 7, Pa *Associate in Physiology* (1, 1946)
- Waisman, Harry A, M D, Ph D University of Illinois Research Hospital, 1819 W Polk St, Chicago, Ill (2, 1944)
- Wakeman, Alfred J, Ph D Hatfield Hill Road, Bethany, Conn *Retired* (2, 1906)
- Wakerlin, George E, Ph D, M D University of Illinois Medical School, 1853 W Polk St, Chicago *Professor of Physiology* (1, 1933, 3, 1934)
- Wakim, Khalil G, M D, Ph D Mayo Clinic Rochester, Minn (1, 1942)
- Walcott, William W, Ph D Department of Physiology, College of Physicians and Surgeons, Columbia University, New York 32, N Y *Instructor* (1, 1917)
- Wald, George, M A, Ph D Biological Laboratories, Harvard University, Cambridge, Mass (1, 1934)
- Walker, Arthur M, M D University of Pennsylvania, Philadelphia *Associate Professor of Pharmacology, Major, M C* (1, 1932, 3, 1939)
- Walker, Burnham S, Ph D, M D Boston University School of Medicine, 80 E Concord St, Boston, Mass *Professor of Biochemistry* (2, 1940)
- Walker, Ernest Linwood, S D 50 Winchester St, San Francisco, Calif (3, 1931)
- Walker, Sheppard M, M A, Ph D 5511 Cabanne Ave, St Louis, Mo *Department of Physiology, Washington University School of Medicine Assistant Professor of Physiology* (1, 1946)
- Wallace, George B, A M, Sc D (hon) M D 477 First Ave, New York City *Emeritus Professor of Pharmacology, New York University College of Medicine* (1, 1901, 2 1906, 3, 1909)
- Wallen-Lawrence, Zonja, Ph D 4534 W Pine Blvd, St Louis, Mo *Lecturer on Nutrition and Diet, Washington University School of Dentistry* (2, 1937)
- Walter, Annabel W 29 Perry St, New York 14, N Y *Bacteriologist, New York City Dept of Health, Bureau of Labs* (6, 1946)
- Walter, Carl W, M D Harvard Medical School, 25 Shattuck Street, Boston, Mass *Director, Laboratory for Surgical Research, Assistant Professor of Surgery, Harvard Medical School, Senior Associate in Surgery, Peter Bent Brigham Hospital* (4, 1942)
- Walters, Orville S, Ph D, M D McPherson, Kan *Physician* (1, 1936)
- Walton, Robert P, M A, Ph D, M D Medical College of the State of South Carolina, Charleston *Professor of Pharmacology* (3, 1933)
- Walton, Seth T, V M D, M S, Ph D Laboratory, Veteran's Hospital, Oteen, N C *Director of Laboratories and Research* (6, 1936)
- Walzer, Matthew, M D 20 Plaza St, Brooklyn, N Y *Attending in Allergy, Jewish Hospital of Brooklyn* (6, 1924)
- Wang, Chi Che, M S, Ph D Box 332, Vets Administration Hospital, Hines, Ill (5, 1933)



- Wang, Shih-Chun, M D , Ph D Columbia University College of Physicians and Surgeons, 630 W 168th St , New York City *Assistant Professor in the Department of Physiology* (1, 1943)
- Wangeman, Clayton P , B A , M D State of Wisconsin General Hospital, 1300 University Ave , Madison 6, Wisconsin *Assistant Professor of Anesthesiology* (3, 1946)
- Wangensteen, Owen Harding, M D University Hospital, Minneapolis 14, Minn (1, 1947, 4, 1931)
- Ward, Walter E , Ph D , M D Cutter Laboratories, Fourth and Parker Streets, Berkeley 1, Calif *Associate Medical Director* (6, 1947)
- Warner, Emory D , M D Medical Laboratories Bldg , Iowa City, Ia *Professor of Pathology* (4, 1937)
- Warner, Robert C , Ph D New York University College of Medicine, 477 First Ave , New York 16, N Y *Assistant Professor of Chemistry* (2, 1946)
- Warren, Charles O , Ph D , M D The Commonwealth Fund, 41 E 57th St , New York 22, N Y (1, 1941)
- Warren, James V , M D Emory University School of Medicine, Atlanta, Ga *Professor of Physiology, Associate Professor of Medicine* (1, 1947)
- Warren, Madeleine Field, A M , Ph D 9 High Rock St , Needham Mass Harvard School of Public Health, 55 Shattuck St , Boston, Mass *Associate in Physiology* (1, 1933)
- Warren, Shields, M D 195 Pilgrim Rd , Boston, Mass *Pathologist, New England Deaconess Hospital, Assistant Professor of Pathology, Harvard Medical School* (4, 1929)
- Wartman, William Beckman, M D Northwestern Univ , 303 East Chicago Ave , Chicago 11, Ill *Professor of Pathology* (4, 1940)
- Wasteneys, Hardolph, Ph D , F R S C University of Toronto, Toronto, Canada *Professor and Head of Department of Biochemistry* (2, 1915)
- Wastl, Helene, M D Hahnemann Medical College and Hospital, Philadelphia, Pa *Research Associate, Depts of Anatomy and Therapeutics* (1, 1939)
- Waterman, Robert E , B S Schering Corporation, 86 Orange St , Bloomfield, N J *Vice-President* (2, 1940)
- Waters, Ralph Milton, M D 1300 University Ave , Madison, Wis *Professor of Anesthesia, University of Wisconsin* (3, 1937)
- Watson, Cecil J , M D , Ph D Department of Medicine, University Hospital, Minneapolis, Minn *Professor and Head of Department of Medicine* (4, 1941)
- Watson, John B , A M , Ph D , LL D Box 526, Westport, Conn (1, 1907)
- Waud, Russell A , M D , M Sc , Ph D Medical School, University of Western Ontario, London, Canada *Professor of Pharmacology* (1, 1925, 3, 1931)
- Waugh, David F , Ph D Department of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge *Assistant Professor of Physical Biology* (1, 1943)
- Way, E Leong, M S , Ph D George Washington University School of Medicine, Washington, D C *Assistant Professor of Pharmacology* (3, 1947)
- Wearn, Joseph T , M D Lakeside Hospital, Cleveland, O *Professor of Medicine, Western Reserve University, Director of Medicine, Lakeside Hospital* (1, 1921)
- Weatherby, J H , M A , Ph D Dept of Physiology and Pharmacology, Medical College of Virginia, Richmond, Va *Associate Professor of Research Pharmacology* (3, 1941)
- Weber, Clarence J , M D , Ph D University of Kansas Hospitals, Kansas City *Assistant Professor of Research Medicine* (2, 1931)
- Webster, Bruce, M D , C M Cornell University Medical College, 1300 York Ave , New York City *Assistant Professor Medicine, Associate Attending Physician, New York Hospital* (5 1935)
- Weed, Lewis H , A M , M D , Sc D National Research Council, 2101 Constitution Ave , Washington, D C (1, 1919)
- Wégria, René, M D Department of Medicine, Presbyterian Hospital, 622 W 168th St , New York City *Instructor in Medicine* (1, 1941)
- Weichert, Charles K , Ph D University of Cincinnati, Cincinnati, O *Professor of Zoology* (1, 1935)
- Weil, Alfred J , M D Lederle Laboratories, Inc , Pearl River, N Y *Immunologist* (6, 1940)
- Weil, Arthur, M D 161 East 71st St , New York, N Y (1, 1940)
- Weil, Leopold, Ph D Eastern Regional Research Laboratory, U S Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa *Chemist* (2, 1942)
- Weir, Everett G , M S , Ph D School of Medicine, Howard University, Washington, D C *Assistant Professor of Physiology* (1, 1941)
- Weiss, Charles, M S , Ph D , M D Jewish Hospital, York & Tabor Roads, Philadelphia, Pa *Director of Laboratories* (4, 1934, 6, 1920)
- Weiss, Emil, M D , Ph D P O Box 714, Chicago, Ill *Pathologist, Chicago Eye, Ear, Nose and Throat Hospital* (6, 1927)
- Weiss, Paul, Ph D University of Chicago, Chicago, Ill *Professor of Zoology* (1, 1936)
- Welch, Arnold D , Ph D , M D Western Reserve University School of Medicine, Cleveland, O *Professor of Pharmacology* (3, 1942, 5, 1944)

- Welch, Henry, M S, Ph D Rm 6171 S Agriculture Bldg, Washington, D C Chief, Division of Penicillin Control and Immunology, U S Food and Drug Administration (6, 1932)
- Weld, Charles Beecher, M A, M D Dalhousie University, Halifax, N S, Canada Professor of Physiology (1, 1936)
- Weld, Mrs Julia T Collego of Physicians and Surgeons, 630 W 168th St, New York City Research Associate in Pathology (6, 1920)
- Welker, William H, A C, Ph D, D Sc 1853 W Polk St, Chicago, Ill Professor Emeritus of Biological Chemistry, College of Medicine, University of Illinois (2, 1906)
- Weller, Carl Vernon, M D 1130 Fair Oaks Parkway, Ann Arbor, Mich Professor of Pathology and Chairman, Department of Pathology, University of Michigan (4, 1923)
- Wells, Herbert S, M D University of Minnesota Minneapolis 14 Professor of Clinical Physiology (1, 1932)
- Wells, Joseph Albert, M S, Ph D Northwestern University Medical School, Chicago, Ill Associate in Pharmacology (3, 1944)
- Welsh, John H, Ph D Biological Laboratories, Harvard University, 16 Divinity Ave, Cambridge 38, Mass Associate Professor of Zoology (1, 1945)
- Wendel, William B, Ph D Department of Biochemistry, Tulane University School of Medicine, 6501 St Charles Ave, New Orleans 15, La Professor of Biochemistry (2, 1932)
- Werkman, C H, Ph D, D Sc Science Hall, Iowa State College Ames Professor and Head of Department of Bacteriology (2, 1942)
- Werle, Jacob M, M D, Capt, 138 Evacuation Hospital, APO 408, New York, N Y Neurosurgeon (1, 1943)
- Werner, Harold W, Ph D The Wm S Merrell Co, Lockland Station, Cincinnati, O Director of Pharmacology Research (3, 1942)
- Wertenberger, Grace E, S M Ph D Women's Medical College of Pennsylvania Philadelphia Assistant Professor of Physiology (1, 1943)
- Werthessen, Nicholas T, Ph D Shrewsbury, Mass Worcester Foundation for Experimental Biology Senior Fellow (1, 1946)
- Wesson, Laurence Goddard, Ph D Forsyth Dental Infirmary, Boston, Mass Research Biochemist (2, 1929, 3, 1932)
- West, Edward S, M S, Ph D University of Oregon Medical School, Portland Professor of Biochemistry (2, 1925)
- West, Harold D, M S, Ph D Meharry Medical College, Nashville 8, Tenn Professor of Biochemistry and Head of Dept of Biochemistry (2, 1946)
- West, Randolph, M A, M D 622 W 168th St, New York City Associate Professor of Medicine, Columbia University (2, 1931)
- Westerfeld, Wilfred Wiedey, Ph D Syracuse University College of Medicine, Syracuse 10, N Y Professor of Biochemistry (2, 1911)
- Weston, Raymond E, M D, Ph D Medical Division, Montefiore Hospital, New York 67, N Y Assistant in Medicine (1, 1947)
- Weymouth, Frank W, Ph D Stanford University, Calif Professor of Physiology and Executive of the Department (1, 1917)
- Wheeler, George W, M D New York Hospital, 525 E 68th St, New York City Assistant Director (6, 1920)
- Wheeler, Kenneth M, Ph D Bureau of Laboratories, Connecticut State Department of Health, 1179 Main St, Hartford Research Microbiologist (6, 1938)
- Wheeler, Mary W, M A Division of Laboratories and Research, New York State Department of Health, Albany Associate Bacteriologist (6, 1933)
- Wheeler, Ruth, Ph D Vassar College, Poughkeepsie, N Y Professor Emeritus of Physiology and Nutrition (2, 1915, 5, 1933)
- Whelon, Homer, M S, M D American Bank Bldg, Seattle, Wash (1, 1919)
- Whipple, George H, M D, Sc D University of Rochester, Rochester, N Y Professor of Pathology and Dean of the School of Medicine and Dentistry, Member of the National Academy of Sciences (1, 1911, 4, 1913)
- White, Abraham, M A, Ph D 333 Cedar St, New Haven, Conn Associate Professor of Physiological Chemistry, Yale University School of Medicine (2, 1934, 5, 1937)
- White, Florence R, M A, Ph D National Cancer Institute, Bethesda 14, Md Biochemist, National Institute of Health (2, 1946)
- White, Frank D, Ph D, F I C Medical College, University of Manitoba, Winnipeg, Canada Assistant Professor of Biochemistry, Faculty of Medicine (2, 1931)
- White, Harvey Lester, M D Associate Professor of Physiology, Washington University Medical School, St Louis, Mo (1, 1923)
- White, Julius, A M, Ph D National Cancer Institute, Bethesda, Md Head Biochemist (2, 1937)
- White, Paul Dudley, M D, Massachusetts General Hospital, Boston Lecturer in Medicine, Harvard Medical School, Physician (in charge of Cardiac Clinics and Laboratory), Mass General Hospital (3, 1921)
- Whitehead, Richard W, M A, M D University of Colorado School of Medicine, 4200 E Ninth Ave, Denver Professor of Physiology and Pharmacology (1, 1933, 3, 1928)
- Whitehorn, William V, M D Department of

- Physiology, University of Illinois College of Medicine, Chicago (1, 1947)
- Wiener, Alexander S., M D 64 Rutland Rd., Brooklyn, N Y *Bacteriologist and Serologist to Office of Chief Medical Examiner of New York City, Head of Transfusion Division, Jewish Hospital of Brooklyn* (6, 1932)
- Wiersma, Cornelis A G., M A, Ph D California Institute of Technology, Pasadena *Associate Professor of Physiology* (1, 1941)
- Wiggers, Carl J., M D, Sc D Medical School, Western Reserve University, Cleveland, O *Professor and Director of Physiology* (1, 1907, 3, 1909)
- Wiggers, Harold C., Ph D Department of Physiology and Pharmacology, Albany Medical College, Union University, Albany 3, N Y *Professor and Chairman of Department* (1, 1938)
- Wigodsky, Herman S., Ph D, M D Aviation Medical Service, Civil Aeronautics Administration, Washington 25, D C (1, 1943)
- Wikler, Abraham, M D U S Public Health Service Hospital, Lexington, Ky *Surgeon (R), U S Public Health Service* (3, 1944)
- Wilber, Charles G., M A, Ph D The Biological Laboratory, Fordham University, New York 58, N Y *Assistant Professor of Physiology* (1, 1947)
- Wilde, Walter S., Ph D Carnegie Institution of Washington, Department of Embryology, Wolfe and Madison Sts, Baltimore 5, Md *Associate Member* (1, 1944)
- Wilder, Russell M., Ph D, M D Mayo Clinic, Rochester, Minn *Professor of Medicine, Mayo Foundation, University of Minnesota* (1, 1921, 4, 1924, 5, 1933)
- Wiley, Frank H., M S, Ph D Food and Drug Administration, Federal Security Agency, Washington 25, D C *Chemist* (2, 1933)
- Wilhelme, Jane Russell, Ph D Yale University School of Medicine, 333 Cedar St., New Haven, Conn *Instructor in Physiological Chemistry* (1, 1939)
- Wilhelmi, Alfred E., Ph D 333 Cedar St., New Haven, Conn Yale University School of Medicine *Assistant Professor of Physiological Chemistry* (2, 1942)
- Wilhelmj, Charles Martel, M D Creighton University School of Medicine, Omaha, Neb *Professor of Physiology* (1, 1931)
- Wilkerson, Vernon A., M D, Ph D Howard University Medical School, Washington, D C *Professor and Head of Department of Biochemistry* (2, 1936)
- Williams, Carroll M., A M, Ph D, M D Biological Laboratories, Harvard University, Cambridge, Mass *Assistant Professor of Zoology* (1, 1947)
- Williams, Edwin G., M D, D T M, D T H National Institute of Health, Bethesda 14, Md *Senior Surgeon U S Public Health Service, Director of Research, U S P H S Hospital, Lexington, Ky* (3, 1944)
- Williams, Harold H., Ph D Fernow Hall, Cornell University, Ithaca, N Y *Professor of Biochemistry* (2, 1938, 5, 1936)
- Williams, Horatio B., M D, Sc D Box 893, Greenwich, Conn *Dalton Professor of Physiology Emeritus, Columbia University* (1, 1912)
- Williams, J W., M S, Ph D University of Wisconsin, Chemistry Bldg., Madison *Professor of Chemistry* (2, 1944)
- Williams, Ray D., M S, M D 6834 Waterman St., St Louis, Mo *Assistant Professor of Clinical Medicine, Washington University* (5, 1941)
- Williams, Robert Hardin, M D Thorndike Laboratory, Boston City Hospital, Boston, Mass *Associate in Medicine, Harvard Medical School, Assistant Physician, Thorndike Memorial Laboratory, Junior Visiting Physician, II and IV Medical Services (Harvard) Boston City Hospital* (4, 1940)
- Williams, Robert R., M S, D Sc 297 Summit Ave., Summit, N J *Chemical Consultant, Bell Telephone Laboratories* (2, 1919, 5, 1941)
- Williams, Roger J., Ph D, D Sc University of Texas, Department of Chemistry, Austin *Professor of Chemistry, Director, Biochemical Institute* (2, 1931, 5, 1945)
- Williams, William L., M A, Ph D University of Minnesota, Medical School, Minneapolis 14, Minn *Assistant Professor of Anatomy* (1, 4, 1947)
- Wills, J H., M S, Ph D Pharmacology Section, Medical Division, Army Medical Center, Md (1, 1943)
- Wilson, David Wright, M S, Ph D University of Pennsylvania Medical School, Philadelphia *Benjamin Rush Professor of Physiological Chemistry* (1, 1915, 2, 1915)
- Wilson, Frank N., M D University Hospital, Ann Arbor, Mich *Professor of Medicine, University of Michigan* (4, 1925)
- Wilson, Karl M., M D University of Rochester, School of Medicine, Rochester, N Y *Professor of Obstetrics and Gynecology* (4, 1927)
- Wilson, P W., Ph D Department of Agricultural Bacteriology, University of Wisconsin, Madison *Professor in Agricultural Bacteriology* (2, 1939)
- Wilson, Robert H., Ph D U S Dept of Agriculture, Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif *Pharmacologist* (3, 1937)
- Winder, Claude V., Sc D 1927 Dexter Ave., Ann Arbor, Mich *Pharmacologist, Parke, Davis & Company, Detroit, Mich* (1, 1938)

- Windle, William Frederick, Ph D Medical School, University of Pennsylvania, Philadelphia *Professor of Anatomy* (1, 1937)
- Winklerwerder, Walter L F, M D 1011 St Paul St, Baltimore, Md *Associate in Medicine, Johns Hopkins Medical School* (6, 1938)
- Winnick, Theodore, Ph D Division of Biochemistry, Univ of California, Berkeley, Calif *Research Associate* (2, 1916)
- Winter, Charles A, Ph D University of Oklahoma, School of Medicine, 801 E 13th St, Oklahoma City *Associate Professor of Physiology* (1, 1910)
- Winter, Irwin Clinton, Ph D, M D G D Searle & Co, P O Box 5110, Chicago 80, Ill *Director of Clinical Research* (3, 1941)
- Winters, Jet C, M A, Ph D University of Texas, Austin *Professor of Home Economics* (5, 1933)
- Winternitz, M C, M D Yale University School of Medicine, New Haven, Conn *Anthony N Brady Professor of Pathology* (1, 1913)
- Wintersteiner, Oskar, Ph D The Squibb Institute for Medical Research, New Brunswick, N J *Member, Head, Division of Organic Chemistry, Honorary Professor of Biochemistry, Rutgers University* (2, 1930)
- Wintrobe, Maxwell Myer, M D, Ph D University of Utah School of Medicine, Salt Lake City *Professor and Head of the Department of Internal Medicine, Director, Laboratory for the Study of Hereditary and Metabolic Disorders* (1, 1940)
- Winzler, Richard J, Ph D Dept of Biochemistry, Univ of Southern Calif Medical School, Los Angeles 7, Calif *Associate Professor of Biochemistry* (2, 1946)
- Wiseman, Bruce Kenneth, M D Kinsman Hall, Ohio State University, Columbus *Professor and Chairman of Department of Medicine, Assistant Director of Medical Research* (1, 1932)
- Wislocki, George B, M D Harvard University Medical School, 25 Shattuck St, Boston, Mass *Parkman Professor of Anatomy* (1, 1921)
- Witebsky, Ernest, M D Buffalo General Hospital, 100 High St, Buffalo, N Y *Professor of Bacteriology and Immunology* (6, 1935)
- Wittich, Fred W, M D 101 LaSalle Medical Bldg, Minneapolis 2, Minn *Sec-Treas American College of Allergists, Chairman, Executive Committee, International Association of Allergists* (6, 1944)
- Wolbach, S Burt, M D Children's Hospital, Boston, Mass *Shattuck Professor of Pathological Anatomy, Emeritus, Director of Nutritional Research, Children's Hospital* (4, prior to 1920)
- Wolf, Arnold Veryl, Ph D Albany Medical College, Albany, N Y *Assistant Professor of Physiology and Pharmacology* (1, 1916)
- Wolff, Harold G, M D, M A New York Hospital, 525 E 68th St, New York City *Associate Professor of Medicine, Cornell University Medical College, Associate Attending Physician, New York Hospital* (1, 1930, 3, 1912)
- Wolff, William A, M A, Ph D Bowman Gray School of Medicine, Winston Salem 7, N C *Assistant Professor of Biochemistry* (2, 1947)
- Womack, Madelyn, Ph D Foods and Nutrition Division, Agricultural Research Administration, U S Department of Agriculture, Washington 25, D C *Biochemist* (5, 1947)
- Wood, Earl H, M S, Ph D, M D Mayo Aero-medical Unit, Mayo Foundation, Rochester, Minn *Assistant in Physiology* (1, 1943)
- Wood, Harland G, Ph D Department of Biochemistry, Western Reserve University, Cleveland, Ohio *Professor of Biochemistry* (2, 1941)
- Wood, Horatio C, Jr, M D, Ph M 319 S 41st St, Philadelphia, Pa *Professor of Pharmacology and Therapeutics, University of Pennsylvania Professor of Materia Medica Philadelphia College of Pharmacy and Science* (3, 1908)
- Wood, John L, Ph D University of Tennessee School of Biological Sciences, 875 Monroe Avenue, Memphis 3, Tenn *Associate Professor of Chemistry* (2, 1917)
- Woodbury, Robert A, Ph D, M D Department of Pharmacology, University of Tennessee, Memphis *Professor of Pharmacology* (1, 1936, 3, 1941)
- Woods, Alan C, M D Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md *Ophthalmologist-in-Chief, Acting Professor of Ophthalmology, Johns Hopkins University, Director, Wilmer Ophthalmological Institute* (6, 1918)
- Woods, Ella, A M, Ph D University of Idaho, Moscow *Home Economist, Experiment Station* (2, 1925, 5, 1933)
- Woodward, Alvalyn E, M S, Ph D University of Michigan, Ann Arbor, *Assistant Professor of Zoology* (1, 1932)
- Woodyatt, Rollin T, M D 237 E Delaware Place, Chicago, Ill *Professor of Medicine, Rush Medical College, University of Chicago* (2, 1912)
- Woolley, D Wayne, Ph D Rockefeller Institute for Medical Research, 66th St, and York Ave, New York City *Associate Member* (2, 1946, 5, 1941)
- Woolpert, Oram C, M D, Ph D Camp Detrick,

- Friederick, Md *Technical Director, Biological Division, Chemical Corps* (6, 1947)
- Woolsey, Clinton N, M D Johns Hopkins University School of Medicine, Baltimore, Md *Associate Professor of Physiology* (1, 1938)
- Wortis, S Bernard, M D Department of Psychiatry, New York University College of Medicine, New York 16 *Professor of Psychiatry and Chairman of the Department, Director, Psychiatric Division of Bellevue Hospital* (1, 1947)
- Wright, Angus, M D University of Southern California Medical School, 657 S Westlake Ave, Los Angeles *Pathologist, California Hospital* (4, 1935)
- Wright, Arthur W, M D Albany Medical College, New Scotland Ave, Albany, N Y *Professor of Pathology and Bacteriology* (4, 1941)
- Wright, Charles Ingham, M S, Ph D National Institute of Health, Bethesda, Md *Senior Pharmacologist, U S Public Health Service* (1, 1935, 3, 1936)
- Wright, George G, Ph D Div of Infectious Diseases, National Inst of Health, Bethesda, Md *National Research Fellow* (6, 1943)
- Wright, Harold N, M S, Ph D University of Minnesota, Minneapolis *Associate Professor of Pharmacology* (3, 1933)
- Wright, Lemuel D, M S, Ph D Medical Research Division, Sharp and Dohme, Inc, Glenholden, Pa *Research Biochemist* (2, 1946, 5, 1946)
- Wright, Sydney L, M A, Ph D Endsmeet Farm, Wyncote, Pa (2, 1933)
- Wulzen, Rosalind, M S, Ph D Oregon State College, Corvallis *Assistant Professor of Zoology* (1, 1916)
- Wyckoff Ralph W G, Ph D U S Public Health Service, National Institute of Health, Bethesda, Md *Senior Scientist* (6, 1940)
- Wyman, Jeffries, Jr, Ph D Biological Laboratories, Harvard University, Cambridge, Mass *Associate Professor of Zoology* (1, 1928)
- Wyman, Leland C, Ph D 5 Furnival Rd, Jamaica Plain 30, Mass Boston University School of Medicine, Boston, Mass *Associate Professor of Physiology* (1, 1927)
- Wynne, Arthur M, M A, Ph D, F R S C Department of Biochemistry University of Toronto, Toronto, Canada *Professor of Biochemistry* (2, 1940)
- Yerkes, Robert M, Ph D Yale Laboratories of Primate Biology, 333 Cedar St, New Haven, Conn *Professor of Psychobiology, Yale University, Member of the National Academy of Sciences* (1, 1904)
- Yonkman, Frederick F, Ph D, M D Ciba Pharmaceutical Products, Inc, Summit, N J *Director of Research at Ciba and Lecturer in Pharmacology, College of Physicians and Surgeons, Columbia University, New York City* (3, 1931)
- Youmans, William Barton, M A, Ph D, M D University of Oregon Medical School, Portland *Professor of Physiology* (1, 1939)
- Young, A G, Ph D, M D 520 Commonwealth Ave, Boston, Mass *Assistant Professor of Therapeutics, Boston University School of Medicine, Medical Director, Corey Hill Hospital, Brookline* (3, 1925)
- Young, E G, Ph D, F R S C Dalhousie University, Halifax, N S, Canada *Professor of Biochemistry* (2, 1925)
- Youngburg, Guy E, M S, Ph D 66 Park Circle, Eggertsville, Buffalo, N Y *Professor of Biological Chemistry, University of Buffalo* (2, 1927)
- Yuile, Charles L, M D, C M University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd, Rochester, N Y *Associate Professor of Pathology* (4, 1941)
- Zeehmeister, L California Institute of Technology, Pasadena *Professor of Organic Chemistry* (2, 1941)
- Zeekwer, Isolde T, M D School of Medicine, University of Pennsylvania, Philadelphia *Assistant Professor of Pathology* (1, 1934, 4, 1927)
- Zeldis, Louis Jenrette, M D Emory University School of Medicine, Atlanta, Ga *Associate Professor of Pathology* (4, 1945)
- Zimmerman, Harry M, M D Montefiore Hospital, Gun Hill Rd, New York 67, N Y (4, 1933)
- Zittle, Charles A, Ph D Biochemical Research Foundation, Newark, Delaware (2, 1946)
- Zucker, Marjorie B Ph D Department of Physiology, College of Physicians and Surgeons, Columbia University (1, 1947)
- Zweifach, Benjamin W, Ph D Department of Medicine, New York Hospital and Cornell University Medical College, 525 E 68th St, New York 21 *Research Associate* (1, 1945)
- Zwemer, Raymond L, Ph D 5003 Battery Lane, Bethesda 14, Md National Academy of Sciences, 2101 Constitution Ave, Washington 25, D C *Executive Secretary, National Academy of Sciences and National Research Council* (1, 1930)

## SUMMARY OF MEMBERSHIP

The American Physiological Society	1025
American Society of Biological Chemists	755
American Society for Pharmacology and Experimental Therapeutics	378
The American Society for Experimental Pathology	314
American Institute of Nutrition	318
The American Association of Immunologists	298
Total members by Societies	3088

## DECEASED MEMBERS

1917

Abels, Jules C (4) June 13, 1917	Larson, Winford P (6) January 1917
Barcroft, Sir Joseph (1h) 1917	Libman, Emanuel (6) January 1917
Barnett, F C (1) 1917	Mast, S O (1) February 3, 1917
Burrows, Montrose T (1) 1917	Millikan, Glenn A (1) May 25, 1917
Cole, Arthur G (2) July 14, 1917	Plotz, Harry (6) January 6, 1917
Cutler, Elliott C (1) August 16, 1917	Pucher, George W (2) November 20, 1917
Dubin, Harry E (2) June 13, 1917	Schwartz, Erich W (3) November 18, 1917
Green, Robert G (6) September 7, 1917	Talbert, George A (1) April 3, 1917
Greene, Charles Wilson (1, 2, 3) May 1, 1917	Winkler, Alexander Woodward (1) June 26, 1917
Hecht, Selig (1) September 18, 1917	Witzemann, Edgar J (2) November 30, 1917
Johnson, Treat B (2) July 28, 1917	Woodruff, Lorande Loss (1) June 23, 1917





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